Medical Library

FEB 24 1942

AMERICAN HEART JOURNAL

For the Study of the

CIRCULATION

Published Monthly Under the Editorial Direction of
The American Heart Association

Vol. 23 FEBRUARY 1942 No. 2

FRED M. SMITH----------Editor-in-Chief

Associate Editors

HUGH McCULLOCH
HORACE M. KORNS
EDGAR V. ALLEN

EDITORIAL BOARD

CLAUDE S. BECK
NORMAN E. FREEMAN
HARRY GOLDBLATT
GEORGE HERRMANN
WILLIAM J. KERR
ROBERT L. LEVY
H. M. MARVIN
JONATHAN C. MEAKINS
ROY W. SCOTT
ISAAC STARR
J. MURRAY STEELE
PAUL D. WHITE
FRANK N. WILSON
CHARLES C. WOLFERTH
IRVING S. WRIGHT

Published by THE C. V. MOSBY COMPANY, 3525 Pine Blvd., St. Louis, U.S.A.
Copyright 1942 by The C. V. Mosby Company

Contents on Inside Cover

American Heart Journal

For the Study of the Circulation

CONTENTS FOR FEBRUARY, 1942

Original Communications

Peripheral Circulatory Failure. Alfred Blalock, M.D., Baltimore, Md. ---- 147

Cardiology as a Specialty. Paul D. White, M.D., Boston, Mass. ---- 161

The Effect of Sex Hormones on the Production of Ergotamine Gangrene in Rats. Erich Krueger, M.D., John B. Ludden, M.D., and Irving S. Wright, M.D., With Technical Assistance by Julius Wiland, B.S., New York, N. Y. ---- 164

Rheumatic Carditis in a Tropical Country. E. Garcia Carrillo, M.D., San José, Costa Rica ---- 170

The Peripheral Blood Flow in Myxedema as Compared With That in Hyperthyroidism. Harold J. Stewart, M.D., and Willis F. Evans, M.D., New York, N. Y. ---- 175

A Study of the Rate of Water Loss From the Surfaces of the Finger Tips and Toe Tips of Normal and Senile Subjects and Patients With Arterial Hypertension. G. E. Burch, M.D., A. E. Cohn, M.D., and C. Neumann, M.D., New York, N. Y. ---- 185

Infected Thrombi of the Heart. James R. Lisa, M.D., and Cyril Solomon, M.D., New York, N. Y. ---- 197

Syphilitic Cardiovascular Disease and Bacterial Endocarditis. Simon Koletsky, M.D., Cleveland, Ohio ---- 208

Lumbar Sympathectomy in the Treatment of Intermittent Claudication. Norman E. Freeman, M.D., and Hugh Montgomery, M.D., Philadelphia, Pa. 224

Cedilanid, With Special Reference to Its Intravenous Use. Maurice Sokolow, M.D., and Francis L. Chamberlain, M.D., San Francisco, Calif. ---- 243

Clinical Experience With the Oral Administration of Cedilanid, and a Comparison of the Oral and Intravenous Preparations of Cedilanid With Digitalis Purpurea. Francis L. Chamberlain, M.D., and Maurice Sokolow, M.D., San Francisco, Calif. ---- 245

Acute Pericarditis Simulating Acute Coronary Occlusion. Arlie R. Barnes, M.D., and Howard B. Burchell, M.D., Rochester, Minn. ---- 247

Department of Clinical Reports

Sinoauricular Block and Retrograde Auricular Conduction in a Case of Permanent Complete Heart Block. Bruno Kisch, M.D., and Gary Zucker, M.D., New York, N. Y. ---- 269

Department of Reviews and Abstracts

Selected Abstracts ---- 278

American Heart Association, Inc. ---- 290

Vol. 23, No. 2, February, 1942. American Heart Journal is published monthly by the C. V. Mosby Company, 3523 Pine Blvd., St. Louis, Mo. Subscription Price: United States, its Possessions, Pan-American Countries, $10.00; Canada, $11.50 (Canadian Currency); Foreign, $11.00. Entered as Second-Class Matter at Post Office at St. Louis, Mo., under Act of March 3, 1879. Printed in the U. S. A.

American Heart Journal

VOL. 23 FEBRUARY, 1942 NO. 2

Original Communications

PERIPHERAL CIRCULATORY FAILURE

ALFRED BLALOCK, M.D.
BALTIMORE, MD.

THE honor of being asked to give the George E. Brown Memorial Lecture for 1941 is appreciated very greatly. Brown, who, like Banting, and others, left a small community in order to put his new ideas to a more rigid test, shall be remembered as a notable contributor to the art and science of medicine. It is particularly fitting that this society should honor his memory, because his greatest interest was in the field of vascular disease.

To cover the entire field of shock, or peripheral circulatory failure, even if I were capable of performing the feat, would be obviously too great a task for this brief lecture. Much that might be said must be omitted, and for this I beg your forgiveness. A detailed consideration of the subject can be found in monographs by Cannon,[1] Moon,[2] Scudder,[3] and Blalock,[4] and in a recent review by Harkins.[5]

It is agreed that Cannon[1] is correct in his statement that definition is not a prime requisite in such a complex as shock. Granting that no definition is entirely adequate, one may state that shock is a condition of peripheral circulatory failure brought on by a discrepancy between the volume of circulating blood and the size of the vascular system and leads to a deficient blood supply to the tissues of the body. This discrepancy may be due to a reduction of the blood volume, or to an increase in the capacity of the vascular system, or to both. The combination of alterations almost certainly occurs more often than has been suspected.

Even though definition is not a prime requisite, it is important that the clinical picture should be familiar to all, and careful descriptions are available. There is no difficulty in recognizing the fully developed condition, but, unfortunately, there is no known certain index as to the condition of the circulation in early or incipient shock. Determinations of the pulse rate and of the concentration of the erythrocytes are usu-

George E. Brown Memorial Lecture, Seventeenth Meeting of the American Heart Association, Cleveland, Ohio, May 31, 1941.
Received for publication Sept. 6, 1941.

ally of value in this respect, but either or both may be misleading. Unfortunately, the arterial blood pressure usually does not decline greatly until after rather marked changes in the circulation have occurred. Even though the arterial pressure is not a good guide to the condition of the circulation in incipient shock, it is the best available index to the state of affairs in shock that is more fully developed.

It is important to remember that not all declines of blood pressure are of the same significance. There is a vast difference between two patients, both with a blood pressure at the critical level, when one has cold extremities and the other has warm or only slightly cool extremities. The patient who has a low arterial pressure and cold extremities usually has arterial vasoconstriction secondary to a significant reduction in the blood volume. The prognosis is usually very grave unless a sustained elevation of the decreased blood volume can be brought about by appropriate therapy. On the other hand, the situation is not so grave when the person with a low blood pressure has no significant reduction in blood volume. Vasodilatation, instead of vasoconstriction, is present, and the condition will usually clear up spontaneously or will respond to vasoconstrictor drugs. Some patients present a combination of the two types, i.e., both a diminution of the blood volume and vasodilatation are present. These various types will be discussed in more detail subsequently.

This paper is concerned in the main with the type of disturbance in which there are a diminution in the blood volume and vasoconstriction; in other words, so-called traumatic, or wound, or secondary, or hematogenic shock.

TERMINAL ALTERATIONS IN SHOCK

There are many causes of shock, but, regardless of the cause, the terminal alterations are very much the same, providing there is an inadequate supply of blood and oxygen for the tissues for an extended period. If a patient dies almost immediately as a result of bleeding from a wound of a large vessel, it is only natural that the tissues of the body should appear anemic at autopsy. On the other hand, if death occurs several hours later, following an extended period of anoxia, a different picture is presented. It simply happens that the anemic appearance of the tissues is encountered more frequently because patients who succumb as a result of uncomplicated hemorrhage from a large vessel usually do so almost immediately.

A prolonged period of an inadequate supply of blood to the tissues was produced in unanesthetized animals by the simple withdrawal and replacement of blood.[6] There was no bodily trauma and no toxins were introduced. After maintaining the blood pressure and blood volume at low levels for several hours, the animals died *despite the fact that more blood was introduced than had been removed.* An increase in the concentration of the blood occurred, and capillary congestion and hemor-

rhage were found on examining the tissues. These changes, which have been believed to indicate "toxemia," may be simply the result of long-standing tissue anoxia.

The particular significance of these experiments is that they remove some of the mystery with which shock has been surrounded. The results throw no light on the question whether the etiological agent in different cases is the absorption of toxins or nociceptive nervous stimuli, or the local loss of blood and fluid or other causes, but they show that the alterations usually encountered in secondary shock can be caused by a simple, marked reduction of the blood volume of unanesthetized animals. It is not necessary to assume that the vital spirits have been exhausted, or that the body of the patient in shock is a big wheal, as some observers have contended. It is important to realize that a prolonged, inadequate supply of blood and oxygen, whether due to the loss of whole blood or plasma, and whether the loss is local or widespread, will result in alterations in the tissues of the body, providing the subject lives long enough for the changes to occur.

PATHOGENESIS

There should be little dispute as to the nature of the terminal manifestations of shock, providing one takes into account the length of time that the circulation has been inadequate, but there is a justifiable difference of opinion as to the cause of the diminution in the blood volume. In the first place, there are many causes of shock, and the same cause is not predominant in all cases. This fact does not minimize the importance of ascertaining the main initiating agent or agents in different types of shock, for it is only in the early stages that distinctive characteristics can be identified, and it is only in the stages before irreversible changes have occurred that treatment is effective.

The problems of pathogenesis and treatment are made more difficult because a standard method for producing a given degree of peripheral circulatory failure is not available. There is no scarcity of methods for producing shock, but one cannot predict with certainty the effects of the removal of a certain quantity of blood, or of the injection of a given dose of histamine, or of the infliction of a known number of blows with a blunt instrument. In other words, there is such a large individual variation in the reactions of different animals to the various shock-producing measures that the interpretation of studies on pathogenesis is difficult, and it is almost impossible to evaluate the effectiveness of various therapeutic procedures unless the agent causes dramatic changes.

To be more specific, normal unanesthetized dogs vary somewhat in their responses to the removal of large quantities of blood. The same is true of the effects of trauma on anesthetized dogs. The skeletal muscles of some animals become macerated very easily when severe trauma

is inflicted, whereas those of other animals are very resistant to trauma. As for the injection of toxic agents, one dog may survive several times the dosage that is fatal to another healthy dog of similar size. As stated previously, this renders the study of the problem of therapy particularly difficult.

The replies to a questionnaire which was sent recently to various investigators in this field indicate that there is no agreement as to the best method of producing shock, and most of them expressed the need for a standard procedure. As a matter of fact, it would appear that we are in need of a standard animal rather than a standard procedure, for it is the individual variations of animals that complicate the interpretation of results. The same may be said, however, of the study of most problems. On the other hand, one may take consolation from the fact that man varies as greatly as the experimental animal in his response to hemorrhage, trauma, and infections, and the individual factor is inescapable.

In spite of the individual variation in response to hemorrhage, I believe that the most easily controlled method for the production of shock is the removal of blood. The most serious objection to the method is that most persons in shock have lost a greater proportion of plasma than of erythrocytes. Due to the fact that all dogs of the same weight do not react identically to the loss of the same quantity of blood, it appears to me that one should remove blood (0.5 to 1 per cent of body weight) at thirty-minute intervals until a sustained decline in arterial pressure to approximately 75 mm. Hg has resulted. In other words, one should use as the standard the reduction of the blood pressure to a given level, rather than the removal of a predetermined quantity of blood. If the latter scheme is used, one should follow the advice of Gregersen, i.e., use a standard breed dog, ascertain the blood volume of each dog, and remove a certain percentage of the blood volume.

If one wishes to cause traumatic shock, it appears to me that traumatization of one of the two posterior extremities is the method of choice. As Cannon[1] has pointed out, the opposite extremity can be used as the control. The same may be said of the use of one side of the body in studies on burns. For the study of the effects of toxic substances, the use of histamine presents certain advantages. In any case, whether one uses these or other available methods, one should remember that the effects of all anesthetic agents are not identical and that this factor should be controlled as accurately as possible. Furthermore, if the experiments are of several days' duration, and if the use of an anesthetic agent is necessary, the ill effect of the agent may be greater than that of the procedure which one is employing.

In spite of the fact that the methods leave much to be desired, certain pertinent observations have resulted from their employment and from clinical studies. Certain of the many theories of shock have been more

or less discarded in recent years, whereas greater attention has been focused on others. In most instances, however, it has been a question of assessing the relative merits of the various theories, rather than entirely excluding some of them. For example, it appears fairly definite that fat embolism may, and does, cause shock, but it is one of the more infrequent etiological agents. Rated in order of increasing importance in explaining the initial alterations in shock, in my opinion, are (1) the hypothesis of toxemia, (2) the theory of disturbed function of the nervous system, and (3) the theory of the local loss of blood and fluid. It should be emphasized that this statement applies to initiating rather than sustaining factors, for it is generally recognized that a general increase in capillary permeability takes place after the blood volume and blood pressure have been depressed for a considerable period. Additional consideration will be given to these three theories.

THEORIES

1. Toxemia Theory

The toxemia theory is founded, in the main, upon indirect evidence gained in the study of human beings and animals. No attempt will be made to review the great bulk of evidence which supports this theory. It was the prevailing theory at the conclusion of the last war, and it still has many supporters. There is no doubt that snake venom and many other toxins, as used by Moon[2] and others, will produce shock, but this does not prove that such products are the cause of traumatic shock. In regard to the original experiments which contributed the main evidence for the toxemia theory, Dale[7] stated several years ago: "With regard to the possible role of histamine, we know now what we did not know then, that of all the major tissues of the body, the muscles contain least of that substance. Whatever else it may have been, the shock following the Bayliss-Cannon limb trauma was not histamine poisoning." This statement, however, should not be interpreted to mean that there may not be slowly acting decomposition products which exert ill effects. The statement regarding the toxemia theory which Cannon[8] made a few years ago appears to be a very sound one. "And even though we may not have devised experiments which demonstrate the presence of any shock-inducing chemical agent, there still remains the clinical testimony, mentioned above, that material absorbed from dead and dying tissues and distributed in the organism may be toxic—so toxic as to play a role in lessening the quantity of circulating blood. It seems unwarranted, therefore, to exclude from further consideration the view that traumatic shock may be, at least in part, a resultant of toxemia."

It is my impression that toxemia has not been excluded as a cause of shock following trauma, but I do not believe that it is a frequent initiating factor. In discussing the etiology of shock in association with

burns, Aldrich[9] stated that, when there is no infection, there is no toxemia. Even though I agree in the main with Aldrich, it is my opinion that the action of toxins, unaccompanied by infection, has not been excluded as a cause of some of the ill effects. At the same time, the evidence[10] indicates that the main cause for the reduction in the blood volume in the first two days after a burn is the local loss of plasma. This is particularly important because it is known that most fatalities which follow burns occur in the first two days. These statements are not meant to imply that toxemia is not a cause of shock, but rather that it is probably not a frequent initiating factor.

2. Nervous Theory

The nervous theory has not received the attention in recent years which its importance deserves. It is a particularly difficult viewpoint to attack experimentally because anesthesia is a necessary prerequisite to the infliction of trauma, and the responses are altered somewhat by the administration of an anesthetic agent. The various factors which may affect vascular tone were admirably presented by Cannon[11] in the first George E. Brown Memorial Lecture, and no attempt will be made to consider them in detail in this lecture.

Until relatively recently, the most important theory of the neurogenic production of shock was that the vasoconstrictor center was exhausted. During the past twenty-five years a number of observers have found that this is not the case, that the center will react to stimuli, and that the arteries are constricted in the earlier stages of secondary shock. It is a new idea, expressed in particular by Freeman,[12] that overstimulation of the sympathetic adrenal system is a frequent cause of shock. It has been pointed out that fear, anger, pain, cold, and mental stress cause stimulation of the sympathetic system. It is known that vasoconstriction is the compensatory response to hemorrhage. Although they admitted that sympathectomized animals withstand hemorrhage less well than normal ones, Freeman and his associates[13] found that the former type of animal is better able to tolerate prolonged depression of the blood pressure. Freeman is of the opinion that, in the production of shock, the activity of the sympathetic system causes intense vasoconstriction, peripheral asphyxia, and capillary dilatation. This theory has much to commend it, but it remains to be shown that uncomplicated vasoconstriction alone will result in shock. It is not vasoconstriction, per se, but rather the diminution in the blood flow to the tissues that results in disastrous changes. Patients and animals with hypertension may have intense vasoconstriction, but none of the manifestations of shock are present. The role of vasoconstriction in the causation of shock is probably that of an augmenting agent, rather than that of a main initiating factor. It is difficult to believe that the body is provided with a protective mechanism against hemorrhage which so readily results in harm when its aid is most needed.

It is believed that stimulation of afferent nerves may cause inhibition as well as stimulation of the sympathetic system. O'Shaughnessy and Slome[14] found that it was more difficult to produce shock by mechanical injury to an extremity if the nervous pathways were blocked. If this observation is correct, the question remains whether the anesthesia is protective because of its effect on excessive stimulation or on inhibition of the sympathetic system. At any rate, clinical experience indicates that the induction of spinal anesthesia after a severe crushing injury of the legs is contraindicated. A number of observers, including Cressman and Blalock,[15] have been unable to confirm most of the experimental results of O'Shaughnessy and Slome. They reported a barrage of impulses from the injured part, but Cressman and Benz[16] observed similar impulses on the nontraumatized side. It must be emphasized, however, that the failure to demonstrate with certainty the presence of nociceptive nervous stimuli does not exclude the possibility that the nervous system is an important agent in the causation of shock. It is my impression, however, that it is concerned, in the main, in the genesis of so-called reflex, or primary, shock.

It may not be out of place at this point to mention the fact that the explosion of a bomb may cause death, even though the person is not struck by shrapnel or debris. Hadfield and his colleagues[17] reported ten such cases. In three of these a fatal degree of saturation of the blood with carbon monoxide was found. In two the cause of death was compression asphyxia. In each of the ten cases some degree of capillary hemorrhage into the lung was found. In the four cases in which death was considered to be due entirely to the effects of blast, there was free hemorrhage in large pulmonary areas. They found that the amount of blood extravasated into the lung varied considerably. They are not of the opinion that the pulmonary injury itself could fatally embarrass the circulation. "It seems more likely that blast produces death by interfering with some vital tissue or centre in which, from the extreme rapidity of action, structural changes are unlikely to be found." The results of recent experiments on this problem are of interest.

Zuckerman[18] exposed animals at various distances to blast. The most outstanding lesion was bilateral pulmonary hemorrhage which varied in degree according to the distance of the animals from the charge. They found that it is the pressure wave of blast which bruises the lungs by its impact on the body wall and that this effect can be prevented or diminished if the body is clothed in a suitable material which is able to take up and disperse the pressure wave. Denny-Brown and Russell[19] found recently that cerebral concussion results not from the intensity of the blow on the head but from sudden acceleration caused by the blow. These observations may be pertinent in explaining the effects of blast. If the head is prevented from moving when struck, the phenomenon fails to occur. Acceleration in movement may result in death with-

out macroscopic lesions of the brain stem. They concluded that the nervous effect of a blow is thus due to the physical acceleration directly transmitted to each and every center. In discussing this subject, Fulton[20] stated that the microscopic causes for the symptoms are still obscure but no doubt have to do with some basic intracellular disorganization of the neuron. It is obvious that further work on this interesting condition is indicated.

3. Local Fluid Loss Theory

There is much evidence that local loss of blood and fluid is a frequent and important initiating factor in the causation of shock. It was shown by me[21] and by Parsons and Phemister[22] that the shock which follows severe trauma to an extremity is due, in the main, to the local loss of blood and fluid. The duration of these experiments was hours, rather than days, and the results do not exclude the possibility of action of other agents in injuries of longer duration. At the same time, these experiments were of approximately the same duration as those which furnished the best experimental evidence for the toxemia theory. Although he admitted that local loss of fluid is the most important cause of shock in injuries of this type, Best[23] stated that the volume of the loss is not sufficiently great in all experiments to account for the peripheral circulatory failure. It seems only fair in this connection to repeat that some dogs, even unanesthetized ones, will tolerate the removal of only a relatively small quantity of blood. Anesthesia is necessary for the studies on trauma, and this may in part be responsible for some instances in which death occurs despite the fact that the local loss of fluid in response to trauma is not great enough by itself to account for the decline of blood pressure.

Freedman and Kabat[24] and Cullen and Freeman[25] have found that shock may be produced by traumatization of extremities which are bound by tape in such manner that the local loss of fluid is restricted. In most of these experiments the local loss of fluid was not sufficiently great to account for the peripheral circulatory failure. The explanation for this is not apparent. It seems only fair to state, however, that the clinical implications are not very great because patients who are injured do not have their extremities protected against the local loss of blood and fluid in this manner. The experiments may be of significance in connection with patients who are pinned beneath objects, as in some air raids, from which they cannot escape.

The local loss of fluid which accompanies severe trauma consists, in the main, of whole blood, although there is a somewhat larger proportion of plasma than of erythrocytes. Milder injuries result primarily in the loss of plasma. Burns are a striking example of this type of injury. The protein content[26] of fluid which accumulates at the site of a burn is practically identical with that of the plasma in the blood vessels. In burns of approximately twenty-four hours' duration,

I found that the local loss of plasma was sufficient by itself to account for a reduction of the blood pressure.[10] It is not maintained that all deaths which follow burns are due solely to the local loss of plasma, but it is maintained that this loss is the most important cause of the shock which may follow a severe burn. This fact assumes added importance, when it is recalled, as Mitchiner[27] has emphasized, that 80 per cent of the deaths which result from burns occur within the first two days.

Although there are many instances of shock which cannot be explained by the local loss of blood and fluid, it is my impression that this loss is the most important and the most frequently encountered of the initiating factors which result in a decline of the blood volume and in traumatic shock. Points in favor of this theory are that the etiological agent is measurable under controlled conditions, and one does not have to assume the presence of some substance such as a hypothetic toxin. Furthermore, it is to be hoped that such a theory is correct from a therapeutic viewpoint, in that replacement treatment affords a better outlook than combating a hypothetic toxin or some other unknown agent.

At the conclusion of the last war, great stress was placed on the institution of measures which would result in a reduction of the absorption of toxins. It is only fair to state that therapy included the intravenous administration of blood and blood substitutes. At the same time, this latter form of therapy was used only sparingly, as compared with today. The best clinical study of shock that has been reported recently is that of Whitby,[28] and associates, of Bristol, England. They report, in detail, twenty-four cases of severe secondary shock which resulted from injuries in air raids. A typical example is the following, in which therapy included the administration of three pints of plasma and four pints of whole blood.

"Case 3. Male, aged 24. Seen 3½ hours after injury. Multiple small injuries of back, legs and arms, gaping hole in right buttock nine inches in diameter, buttock almost completely removed, perforating wound left wrist joint. Morphia gr. ¼ 1¼ hours after injury. Warmed with electric blanket for 1¼ hours before transfusion. Mentally clear, pain ++, thirst +, pallor ++, cyanosis ++, sweating slight, temperature 95° F., pulse 82, blood pressure 40/30, hemoglobin ear 120%, vein 100%, hematocrit 43%.

"After 1 pint plasma in 20 minutes pulse 100, blood pressure 70/40. After 2nd pint plasma in 20 minutes pulse 120, blood pressure 80/45. After 3rd pint plasma in 20 minutes pulse 128, blood pressure 100/55, hemoglobin, ear 80%. Greatly improved but pallor still extreme; 1 pint blood given in 30 minutes, pulse 120, blood pressure 100/60. Started bleeding from buttock; 1 pint blood given in 30 minutes. During operation of debridement at which much bleeding 2 further pints blood administered, each in 15 minutes. Anaesthetic G.O.E. After operation pulse 110, blood pressure 112/70. After 24 hours general condition good; pulse 120, blood pressure 115/80, hemoglobin 78%."

Several points which were made by Whitby and his associates are worthy of consideration in greater detail. They found that the blood pressure is the most reliable measurable indication of the severity of

secondary shock and that other clinical manifestations are variable and not quantitative. The pulse rate was unreliable. It was noted that the cardinal symptoms of shock can be present without much hemoconcentration. In regard to the cause for the decline of blood volume, they make the following statement: "In all cases seen by us it has appeared that the loss of blood volume can be accounted for by external loss and by extravasation into the injured area. In no case has there been evidence to suggest loss of plasma in regions remote from a seat of injury." These observations afford strong evidence in favor of local loss of blood and fluid as an important agent in the causation of traumatic shock. At the same time, I wish to emphasize again the point that there are other causes of shock.

CLASSIFICATION OF PERIPHERAL CIRCULATORY FAILURE

For purposes of clarity, this consideration will be from the viewpoint of pure types and mixed types, admitting that pure is a relative, rather than an absolute, term.

Pure Types.—The terms[29, 30] that are used to designate the different types are hematogenic, neurogenic, and vasogenic. Synonyms for hematogenic are secondary, or traumatic, or wound shock, and it is with this type that this paper is mainly concerned. There are a decrease in the blood volume, vasoconstriction, a decrease in the cardiac output, and subsequently a decline in the blood pressure. The local loss of blood and fluid is the most frequent initiating factor. Examples of this type are external hemorrhage, bleeding into the pleural and peritoneal cavities, loss of blood and fluid into the tissues as a result of trauma, and loss of plasma at the site of a burn.

In the neurogenic type there is vasodilatation which is dependent on diminished constrictor tone as a result of influences acting through the nervous system. Examples of this are so-called primary shock and the conditions which may result from transection of the cervical cord or from the injection of an excessive amount of a spinal anesthetic agent. In the vasogenic type the vasodilatation is produced by agents which act directly on vessels. The injection of histamine produces this type of alteration.

Mixed Types.—As stated previously, many instances of shock are very complicated, and a number of causes are responsible. It is not always possible to ascertain which is the most important of the initiating factors. For example, many different factors may enter into the production of the shock which may accompany surgical operations. Included among these are the pre-existing illness, dehydration, primary psychogenic and neurogenic depressor reactions, hemorrhage, sweating, anesthesia, loss of plasma from exposed surfaces, pooling of blood in damaged areas, infection, and toxemia. Similarly, the mechanism of the peripheral circulatory failure which may result from peritonitis may

be very complicated. The stagnation of blood in dilated blood vessels in the enormous peritoneal surface, the loss of fluid from these vessels, and toxemia are probably the main contributing factors to the peripheral circulatory failure. A diminution of blood volume as a result of dehydration is undoubtedly one of the factors of importance in the causation of the shock which may occur in diabetic acidosis.

Peripheral circulatory failure is an ever present danger in severe, acute infections. Except in rheumatic fever and diphtheria, failure of the peripheral circulation, rather than cardiac insufficiency, is the more frequent cause of death. It is only the previously damaged heart that is likely to fail during an acute infectious disease. Unfortunately, information concerning the mechanism of peripheral circulatory failure in the acute infections, such as pneumonia and typhoid fever, is very meager. It is likely that there is a diminution in the circulating blood volume. This may be due to injury to the capillaries by toxic substances, with consequent stagnation of blood in dilated vessels, and extravasation of plasma.[31] Anoxemia alone may be responsible for the injury to the capillaries. The loss of plasma into the pneumonic areas is probably in part responsible for the peripheral circulatory failure of pneumonia. It is obvious that our information on the nature of the peripheral circulatory failure in acute infections is very meager and that additional studies are indicated.

ACUTE FAILURE OF THE HEART

Many of the clinical features of peripheral circulatory failure may be produced by heart failure of sudden onset. There may be considerable difficulty, for example, in determining whether a patient with abdominal pain and the clinical picture of shock has coronary thrombosis or circulatory failure of peripheral origin. Harrison[30] has stated that, from the viewpoint of pathogenesis, the symptoms of heart failure belong to two groups—those due to engorgement resulting from backward failure and those due to inadequate cardiac output, or forward failure. In acute failure of the heart, forward failure dominates the picture and evidences of passive engorgement are not very prominent.

Since the methods of treatment of central and of peripheral circulatory failure are different, a correct diagnosis is very important. In this differentiation, direct and indirect evidence is helpful. Direct evidence of heart failure includes the presence of venous engorgement or signs of pulmonary congestion. These alterations are not very marked in the acute stage. Abnormal fullness of the veins excludes shock and indicates heart failure. However, abnormal emptiness of the veins, which is always present in shock, may be found in heart failure if the congestion is limited to the pulmonary system. In the latter instance, dyspnea and orthopnea, usually, but not necessarily, associated with râles in the lungs, are observed. The patient with heart failure prefers the sitting

position; this is not true of the patient in shock. The indirect evidence consists chiefly of associated symptoms and signs pointing toward some likely cause of either peripheral circulatory failure or of heart failure. For example, the presence of peritonitis or intestinal obstruction is suggestive of circulatory failure of peripheral origin, whereas the manifestations of coronary thrombosis or of intrapericardial fluid point toward heart failure as the probable cause.

TREATMENT OF PERIPHERAL CIRCULATORY FAILURE

No attempt will be made to discuss the problem of therapy in detail. It is obvious that every effort should be made to prevent the development of shock. The avoidance of dehydration is one of the most important points in this connection. It has been estimated that the total amount of the secretion into the intestinal tract of an adult is approximately 8 liters per day. When it is realized that most of these secretions may be lost by persistent vomiting or diarrhea, and when it is further realized that the total volume of blood plasma is less than 4 liters, the importance of the replacement therapy becomes evident.

The single, most important therapeutic procedure in the treatment of traumatic shock consists of the intravenous introduction of whole blood, plasma, or serum. The vasoconstrictor drugs, which are useful in the therapy of neurogenic shock, are not indicated in secondary shock. In the combination of neurogenic and secondary shock, small doses of vasoconstrictor drugs may be helpful. Solutions of crystalloids are indicated in the treatment of dehydration, but large quantities of these should not be administered intravenously to patients who have sustained severe damage to their capillaries as a result of direct injury or anoxemia. The introduction of large quantities of noncolloidal solutions under these circumstances may result in an additional loss of protein[32] and a decrease in the osmotic pressure. Hemoconcentration is present in most instances of shock, and the greatest need is for plasma, rather than erythrocytes.[33] Plasma and serum present the additional advantage that compatibility tests are not necessary, and there is less delay in instituting treatment than if whole blood is used. Recent work indicates that serum presents certain advantages over plasma if a prolonged period of storage is contemplated.

As stated previously, diminution of the blood volume and vasoconstriction are prominent features of secondary shock. These alterations result in cold extremities. It should be remembered that there is not an equal reduction in blood flow throughout the body and that the extremities are cold, in part at least, because some of their circulation is diverted to more vital structures, such as the brain, heart, and adrenals. Further, it should be noted that the internal temperature may not be depressed, even when that of the extremities is low. It has been observed clinically that the condition of patients in shock may become

worse if intensive efforts are made to elevate the skin temperature. Mason and I[34] found recently that animals in shock as a result of hemorrhage or trauma survive longer with a depressed than with a significantly elevated skin temperature. It is not our impression that cold applications should be used in the treatment of patients in shock, but rather that the skin temperature should not be raised by applying hot water bottles and other heating devices unless the reduction of blood volume is relieved by the introduction of blood or plasma.

The use of inhalations of high concentrations of oxygen has been advocated in the treatment of shock. The results in treating traumatic shock have not been as encouraging in our hands as had been anticipated. This form of therapy is indicated particularly in the peripheral circulatory failure which accompanies pneumonia or intestinal distention.[35] A form of therapy upon which much work is being performed at present is the use of adrenal cortical extract. Active preparations have been available for only a few years, and it is difficult, as yet, to assess their value. In shock due mainly to the loss of sodium chloride and water, this form of therapy appears to be of value. It remains to be ascertained whether adrenal cortical extract and desoxycorticosterone acetate are of value in reducing the permeability of damaged capillaries. Many encouraging reports have appeared recently, and the results of further studies are awaited with interest.

In closing, I should like to repeat that the mechanism responsible for the development of some types of peripheral circulatory failure is fairly well understood but that information on other types is scanty. The available clinical and experimental evidence indicates that local loss of fluid is the most frequent initiating factor and that replacement of the escaped blood and fluid is usually the most effective therapeutic procedure. There are, however, many causes of shock, and attempts to explain all instances by one cause result only in confusion. One is not justified in assuming that all forms of shock are produced in the same way, and hence dogmatic statements regarding therapy may be in error. There are, therefore, many unanswered questions, and it is to be hoped that some future George E. Brown lecturer will be able to report a solution of many of the perplexing problems.

REFERENCES

1. Cannon, W. B.: Traumatic Shock, New York, 1923, D. Appleton & Co.
2. Moon, V. H.: Shock and Related Capillary Phenomena, New York, 1938. Oxford University Press.
3. Scudder, John: Shock. Blood Studies as a Guide to Therapy, Philadelphia, 1940, J. B. Lippincott Co.
4. Blalock, Alfred: Principles of Surgical Care. Shock and Other Problems, St. Louis, 1940, The C. V. Mosby Co.
5. Harkins, H. N.: Recent Advances in the Study and Management of Traumatic Shock, Surgery **9**: 231, 447, 607, 1941.
6. Blalock, A.: Shock. Further Studies With Particular Reference to Effects of Hemorrhage, Arch. Surg. **29**: 837, 1934.
7. Dale, Sir Henry: Discussion on Traumatic Shock, Proc. Roy. Soc. Med. **28**: 1493, 1935.

8. Cannon, W. B.: A Consideration of Possible Toxic and Nervous Factors in the Production of Traumatic Shock, Tr. Am. S. A. **52**: 123, 1934.
9. Aldrich, R. H.: Role of Infection in Burns. Theory and Treatment, With Special Reference to Gentian Violet, New England J. Med. **208**: 299, 1933.
10. Blalock, A.: Experimental Shock. Importance of Local Loss of Fluid in Production of Low Blood Pressure After Burns, Arch. Surg. **22**: 610, 1931.
11. Cannon, W. B.: Factors Affecting Vascular Tone, Am. Heart J. **14**: 383, 1937.
12. Freeman, N. E.: Decrease in Blood Volume After Prolonged Hyperactivity of Sympathetic Nervous System, Am. J. Physiol. **103**: 185, 1933.
13. Freeman, N. E., Shaffer, S. A., Schecter, A. E., and Holling, H. E.: Effect of Total Sympathectomy on Occurrence of Shock From Hemorrhage, J. Clin. Investigation **17**: 359, 1938.
14. O'Shaughnessy, L., and Slome, D.: Etiology of Traumatic Shock, Brit. J. Surg. **22**: 589, 1935.
15. Blalock, A., and Cressman, R. D.: Experimental Traumatic Shock. Further Studies With Particular Reference to Role of Nervous System, Surg., Gynec. & Obst. **68**: 278, 1939.
16. Cressman, R. D., and Benz, E. W.: Nerve Action Potentials in Experimental Traumatic Shock, Arch. Surg. **39**: 720, 1939.
17. Hadfield, G., Swain, R. H. A., Ross, J. M., and Drury-White, J. M.: Blast From High Explosive, Lancet **239**: 478, 1940.
18. Zuckerman, S.: Experimental Study of Blast Injuries to the Lungs, Lancet **239**: 219, 1940.
19. Denny-Brown, D., and Russell, W. R.: Experimental Cerebral Concussion, J. Physiol. **99**: 153, 1940.
20. Fulton, J. F.: Neurology and War, Tr. & Stud., Coll. Physicians, Philadelphia **8**: 157, 1940.
21. Blalock, A.: Experimental Shock. The Cause of Low Blood Pressure Produced by Muscle Injury, Arch. Surg. **20**: 959, 1930.
22. Parsons, E., and Phemister, D. B.: Haemorrhage and "Shock" in Traumatized Limbs, Surg., Gynec. & Obst. **51**: 196, 1930.
23. Best, C. H.: Personal Communication, 1941.
24. Freedman, A. M., and Kabat, H.: The Pressor Response to Adrenalin in the Course of Traumatic Shock, Am. J. Physiol. **130**: 620, 1940.
25. Cullen, M. L., and Freeman, N. E.: A Technique for the Measurement of Local Fluid Loss in Experimental Traumatic Shock, Surgery **10**: 770, 1941.
26. Beard, J. W., and Blalock, A.: Experimental Shock. Composition of Fluid That Escapes From Blood Stream After Mild Trauma to Extremity, After Trauma to Intestines, and After Burns, Arch. Surg. **22**: 617, 1931.
27. Mitchiner, P. H.: Treatment of Burns and Scalds, With Especial Reference to Use of Tannic Acid (Hunterian Lecture), Lancet **1**: 233, 1933.
28. Kekwick, A., Marriott, H. L., Maycock, W. d'A., and Whitby, L. E. H.: Diagnosis and Treatment of Secondary Shock, Lancet **240**: 99, 1941.
29. Blalock, A.: Acute Circulatory Failure as Exemplified by Shock and Hemorrhage, Surg., Gynec. & Obst. **58**: 551, 1934.
30. Harrison, T. R.: Failure of the Circulation, Baltimore, 1935, Williams & Wilkins Co.
31. Fishberg, A. M.: Heart Failure, Philadelphia, 1940, Lea & Febiger.
32. Beard, J. W., Blalock, A., et al.: Intravenous Injections: Effects on Composition of Blood (Four Papers), J. Clin. Investigation **11**: 249, 1932.
33. Levinson, S. O., Neuwelt, F., and Necheles, H.: Human Serum as a Blood Substitute in the Treatment of Hemorrhage and Shock, J. A. M. A. **114**: 455, 1940.
34. Blalock, A., and Mason, M. F.: A Comparison of the Effects of Heat and Cold in the Prevention and Treatment of Shock, Arch. Surg. **42**: 1054, 1941.
35. Fine, J., Sears, J. B., and Banks, B. M.: Effect of Oxygen Inhalation on Gaseous Distention of Stomach and Small Intestine, Am. J. Digest. Dis. & Nutrition **2**: 361, 1935.

CARDIOLOGY AS A SPECIALTY

PAUL D. WHITE, M.D.
BOSTON, MASS.

THE study and treatment of heart disease and the identification of a normal heart are of great importance and wide interest, the prerogative of no individual, group, school, or country. Every doctor and, indeed, every layman is vitally concerned: the obstetrician with the fetal heart action, the pediatrician with the heart of the growing child, the internist with that of the adult, although he often leaves the last ages of man, that is, geriatrics, to the general practitioner, the surgeon with preparation for the strain of operation and aftercare, the military officer with the soldier's heart, and the family doctor and the layman with the entire period from birth to death. A varying degree and kind of knowledge is appropriate for each one of these. The pediatrician does not need to know much about the failing heart of coronary occlusion, with myocardial infarction; the internist and the military surgeon have little knowledge of the puzzling congenital heart problems of infancy; and the family doctor every so often encounters a rare or difficult case of heart disease for the elucidation of which he needs expert help in diagnosis and treatment. Man is not, however, just one age or one problem, any more than he is one organ, and so he must be viewed from every angle on the broad base of interest in him as a whole. It is in this respect that those who are not only interested but also trained in the study of the normal and abnormal heart of man from the cradle, in fact from the womb, to the grave, have a useful role to play, in fact, a role that cannot be, or at any rate has not been, played by any of the other medical workers I have mentioned. That is the role of the cardiologist.

Anyone may be interested in cardiology, may read intensively or extensively on the subject, may attend meetings such as this, or may do research on certain of its problems, but the practicing cardiologist, as such, must do more than this to be worthy of the name, as must obstetricians, surgeons, neurologists, and professors of internal medicine in their respective fields. He must first have a solid foundation, based on training and knowledge in cardiovascular anatomy and physiology. He must have a sound experience and knowledge of medicine in general, and of the vital interrelationships of all organs and systems in the body. He must have knowledge and experience in the judgment and handling

President's Remarks, Seventeenth Scientific Meeting of the American Heart Association, Cleveland, Ohio, May 30, 1941.
Received for publication Sept. 6, 1941.

of personalities, one of the most critical of all attributes of practicing physicians. He must continue to keep abreast of, and have an actual, although necessarily a minor, hand in following (not initiating, of course, except in rare instances) advances in other fields of medicine and surgery and of his profession as a whole. Most important of all, based essentially on all this, he must have had, and he must continue to have, rich, first-hand, constant experience in handling patients with heart troubles, real or imaginary. A general internist does not have time to do this, nor does the family doctor, for, following the old adage, they must learn "less and less about more and more" while the specialist learns "more and more about less and less."

Medicine has become a very extensive profession and requires many different general and special workers. Truly, one field is as important as any other field, whether general practice, teaching, laboratory work and research, administration, or specialization. All of these fields are fascinating to many medical students and young graduates, as they were to me, but one must make a choice, guided often, of course, by opportunity. One cannot now, as one could a generation ago, do everything. To illustrate this point I shall take the liberty of citing my own experience, for I know it best. While still an intern, I appreciated that it was impossible to do all of the things I should like to do in medicine. At first, I was very keen on obstetrics, and then on pediatrics. Later I thought I should like to be a practitioner or professor of general medicine, or a dean. Then came the opportunity, and, with it, the realization of the value of studying intensively in a special field, and so I selected cardiology with my eyes open, realizing that, if I wanted to become well grounded in that field, I could not spend so much time in the other fields. It was as plain as day and has continued to be so ever since. Patient perseverance during a good many years of preparation and of practice has brought me so much satisfaction and happiness that I am eternally grateful to the fates and for the advice I received in the beginning from those who steered me into this career and to those who have helped to keep me there, although I have been tempted frequently to do otherwise in this day and age of restless change. I am also grateful to those who have insisted that I must continue every year to have first-hand knowledge through hospital experience and responsibility in other fields of internal medicine.

I have stated my experience simply as an example of what I believe should be considered an essential for qualification as a special worker in the field of cardiovascular disease. Many of you here today are doubtless internists with a natural interest in heart disease, but without expectation or desire to concentrate primarily on cardiology. Some of you, however, are keen to do so, and to you I urge a program of the most careful grounding and intensive years of preparation, with your feet all the time firmly planted on the ground. We must recognize espe-

cially that electrocardiography, phonocardiography, and other tests of cardiovascular function, both normal and abnormal, are simply parts of the complete whole. To own an electrocardiograph and to perform tests of the rate and volume of the circulation are but small beginnings.

In closing, there is one other point I should like to mention, and that is the occasional remark one hears about the narrowness of specialists. Of course specialists may be narrow, but such a remark as a general observation is erroneous. Broad- or narrow-mindedness, philosophic points of view, and the value of the physician to his profession do not depend upon the particular kind of medical work that is being done; they depend upon the personality, training, industry, and environment of the individual. The family doctor may be broad- or narrow-minded, no matter how *extensive* his knowledge and experience may be; the specialist may be broad- or narrow-minded, no matter how *intensive* his knowledge and experience may be. It is of prime importance, therefore, for the specialist, as well as for the family doctor, to keep closely in touch with broad-minded associates in the field of medicine.

THE EFFECT OF SEX HORMONES ON THE PRODUCTION OF ERGOTAMINE GANGRENE IN RATS

ERICH KRUEGER, M.D., JOHN B. LUDDEN, M.D., AND IRVING S. WRIGHT, M.D., WITH TECHNICAL ASSISTANCE BY JULIUS WILAND, B.S.
NEW YORK, N. Y.

THE observation of McGrath,[1] in 1935, that estrogenic hormone prevents the production of ergotamine gangrene in the tail of female, but not of male, albino rats aroused considerable interest. His results not only stimulated further experimental studies, but also served as a foundation for clinical trial[2] and the increasing use of sex hormones in the treatment of peripheral vascular diseases. In view of the similar anatomic changes in ergotamine gangrene and thromboangiitis obliterans and the rare incidence of the latter disease in women, the observation of McGrath gave rise to speculative considerations as to the importance of a hormonal factor in the etiology of thromboangiitis obliterans.

Suzmann, Freed, and Prag[3] and Ratschow and Klostermann[4] reported confirmatory evidence of McGrath's work. Both groups of investigators, however, extended their studies in different directions from the original studies of McGrath. Suzmann, Freed, and Prag stated that the administration of repeated doses (500 I.U.) of keto-hydroxy-estrone furnished the same degree of protection to castrated male rats as to normal female rats. Ratschow and Klostermann also reported observations on normal and castrated rats of both sexes, including, for the first time, studies on the effect of male sex hormone. Normal male rats were found to be protected by testosterone propionate, but not by estradiol benzoate. The reverse occurred in normal female rats, which were protected by estrogenic hormone, but not by testosterone. In castrated male rats, both female and male sex hormones (the latter to a somewhat lesser degree) prevented ergotamine gangrene. Female castrated rats showed a response only to estrogenic hormone; testosterone rather enhanced the severity of the gangrenous lesions. Further studies by Cobet, Ratschow, and Steckner[5] with synthetic substitutes for follicular hormone, called "diethylstilboestrol," indicated that these compounds did not show the sex-specific action of genuine female sex hormone; they furnished protection to normal female and male rats, and also to

From the First (Columbia University) Division, Welfare Hospital for Chronic Diseases, and the Department of Medicine, New York Post-Graduate Medical School and Hospital, Columbia University.

Aided by a grant from Ciba Pharmaceutical Products, Inc., Summit, N. J.
Received for publication May 24, 1941.

castrated animals of either sex which were subjected to ergotamine administration.

Loewe and Lenke,[6] however, in an attempt to confirm the results of McGrath, were unable, in the first place, to produce gangrene by a single injection of 50 to 100 mg. per kilogram of ergotamine tartrate with a sufficient degree of regularity to satisfy experimental criteria. This was the technique first used by Rothlin,[7] and later by McGrath. Having established a method which would consistently produce gangrene in 100 per cent of the animals by using a minimal dose of 50 mg. per kilogram of freshly prepared ergotamine tartrate solution, given in divided doses over a period of three days, Loewe and Lenke were unable to observe any protective action of estrogenic hormones as measured by incidence, extent, or rapidity of gangrene in normal female, male, and castrated male rats. They used an aqueous solution of theelin in daily injections of 2 to 10 rat units (dosage of McGrath), then 15 to 30 rat units, and, finally, 500 rat units daily of progynon-B in oil. Since a rat unit is considered to be from three to ten times as efficient as an international unit, the latter dosage exceeded that of Suzmann, Freed, and Prag (500 I.U.), and even that of Ratschow and Klostermann (1,000 I.U.).

Because of these contradictory results, further studies to clarify this problem seemed desirable. We were especially interested in the possible effect of testosterone, for no attempt had been made to repeat the experiments of Ratschow and Klostermann. The observation that testosterone was as effective in male rats as estrogen in females seemed of interest, not only experimentally, but also from the practical point of view. These observations also varied somewhat from certain inferences which might be drawn from the results of McGrath. The observation that estrogen prevents ergotamine gangrene was considered as suggestive evidence that female sex hormone might be responsible for the rare incidence of thromboangiitis obliterans in women. Following this line of reasoning, one might expect that testosterone would either remain ineffective or even facilitate the production of ergotamine gangrene.

While our experiments were in progress, Thomas[8] published his observations on the effect of female and male sex hormone on ergotamine gangrene. Using 20 I.U. of theelin daily, he was, like Lowe and Lenke, unable to confirm the results of former investigators. He also included one group of ten female and ten male rats which received testosterone propionate in daily injections of 0.5 mg. This likewise proved ineffective in preventing ergotamine gangrene. However, the dosage chosen by Thomas was only 0.1 of that used by Ratschow and Klostermann.

METHOD

Our experiments were carried out on 155 male and female albino rats of the Wistar strain. These animals were from 60 to 120 days old, and their average

weight was about 150 Gm.; litter mates were distributed evenly in the various groups. The rats which were given Purina dog chow* and water ad lib. were controlled as to weight and normal general appearance for about a week before the experiment was started. Precautions were taken to provide for adequate simultaneous controls in each of five separate experiments.

The tail gangrene was produced by using a commercial preparation of ergotamine tartrate.† In preliminary experiments, both the single large injection used by McGrath and the repeated small injections employed by Ratschow and his collaborators were found to be unsatisfactory for albino rats of the Wistar and Okade strains. Larger single doses produced a high mortality from toxic effects, and daily injections of 0.5 mg., continued for weeks, failed to produce even the slightest changes in the tails of our rats. However, doses of 200 to 300 mg. per kilogram, when given in divided doses of 12.5 mg. per kilogram twice daily, at two-hour intervals, were found to produce gangrene in a large percentage of forty-one rats during preliminary experiments. This method of ergotamine administration was used in our experiments. The rats received two injections daily during a period of eight days, or for a shorter period of time if gangrene appeared earlier. The general toxic effects produced by the first injection of ergotamine tartrate developed within fifteen to sixty minutes and lasted for several hours, after which the animals gradually recovered. Subsequent doses were attended with a gradual decrease in the severity of these general toxic effects, i.e., tolerance seemed to develop. In addition to general weakness, apathy, and changed appearance of the fur, many animals exhibited other symptoms, such as diarrhea and hematuria. Rubor, cyanosis, and pallor at the end of the tail preceded the appearance of gangrene in most of the animals. In some rats, however, the initial changes disappeared and trophic changes, such as loss of hair at the tip of the tail, with localized atrophy of the skin, supervened.

Testosterone propionate,‡ in daily doses of 1.0 mg. and 10.0 mg., and estradiol benzoate, in a daily dose of 0.05 mg., which is equal to 500 I. U., were the preparations used in this study. The substances were administered subcutaneously in dilutions so adjusted that each dose was dissolved in 0.2 to 0.4 c.c. of sesame oil. The control rats were given equivalent doses of plain sesame oil. In some experiments a second group of controls which were receiving no injections other than ergotamine was included. The injections were given daily for seven to ten days before, during, and for seven to ten days after, the period of ergotamine administration.

RESULTS

The results of five separate experiments are shown in Table I.

In Experiment I, gangrene was produced in seven of nine male control rats which were receiving ergotamine according to the technique above described. The administration of 10 mg. of testosterone propionate daily did not prevent the production of gangrene in the male rats of the experimental group; the average extent of the gangrene of the tail was even greater than in the control group. The occurrence of gangrene was 77 per cent for both controls and treated animals.

*Product of the Ralston Purina Co., St. Louis, containing a mixture of grains and alfalfa hay, supplemented by vitamins and minerals.

†The ergotamine tartrate solution (gynergen) was supplied through the courtesy of Dr. Durward Jones, Sandoz Chemical Works, Inc., New York, N. Y.

‡The hormone preparations were supplied through the courtesy of Ciba Pharmaceutical Products, Inc., Summit, N. J.

Experiment II also includes observations on the effect of testosterone on female rats. In this instance, only 1 mg. of testosterone propionate was given daily to six male rats, of which only one developed gangrene only 0.3 cm. in extent; the incidence of gangrene was lowered to 15 per cent. The control group, however, showed a decrease of 40 per cent, for only two of five animals were found to have gangrenous lesions of very slight degree. Upon repeating this experiment with twelve animals in the control and experimental groups (Experiment III), we found that the incidence and extent of gangrene were rather higher in the rats which received testosterone. Female rats treated with different amounts of testosterone (Experiment II) presented no significant difference from controls with respect to the occurrence or degree of gangrenous lesions produced by ergotamine.

TABLE I

EXPERIMENT NO.	DATE	SEX	INJECTION		TOTAL NO. OF RATS	GANGRENE			
			SUBSTANCE	DAILY DOSE		NO. OF RATS	%	AV. EXTENT (CM.)	AV. DAY OF APPEARANCE*
I	Dec., 1939	M	Sesame oil	0.4 c.c.	9	7	77	0.9	8
		M	Test. p.	10 mg.	9	7	77	1.6	7
II	Jan., 1940	M	Sesame oil	0.4 c.c.	5	2	40	0.3	13
		M	Test. p.	1 mg.	6	1	15	0.3	17
		F	Sesame oil	0.4 c.c.	12	5	42	1.2	10
		F	Test. p.	10 mg.	5	2	40	1.1	9
		F	Test. p.	1 mg.	6	3	50	0.7	12
III	Feb.	M	Sesame oil	0.4 c.c.	12	8	67	1.2	14
		M	Test. p.	1 mg.	11	8	73	1.9	9
IV	March	M	None		3	1	33	0.2	10
		M	Sesame oil	0.4 c.c.	10	6	60	0.5	11
		M	Estr. b.	0.05 mg.	10	2	20	0.3	14
		F	None		3	0	0		
		F	Sesame oil	0.4 c.c.	10	0	0		
		F	Estr. b.	0.05 mg.	9	0	0		
V	May	M	Sesame oil	0.4 c.c.	10	6	60	0.9	11
		M	Estr. b.	0.05 mg.	9	7	77	0.5	9
		F	Sesame oil	0.4 c.c.	9	7	77	1.1	7
		F	Estr. b.	0.05 mg.	7	6	85	1.0	12

*Days after the initiation of ergotamine injections.
Test. p., Testosterone propionate; Estr. b., estradiol benzoate.

Having observed no protective effect of male sex hormone against ergotamine gangrene in male and female albino rats, we proceeded to study the effect of estrogenic hormone. In Experiment IV, ten female rats which received estradiol benzoate (0.05 mg. daily) were found to be free from gangrenous lesions, but thirteen female control rats also showed absence of gangrene. Male animals treated with the same daily dose of estrogenic hormone also exhibited a low incidence of gangrene. Only two of ten animals were affected, whereas the control group showed a higher percentage. In repeating the experiment (Experiment V), we found that male and female rats which received estrogen showed a higher incidence of gangrene than their respective group of controls.

There was, furthermore, no evidence that the general toxic effects produced by ergotamine tartrate were less pronounced in those rats which received male or female sex hormones. As a matter of fact, the highest number of deaths was recorded in a group of female rats which received estrogenic hormone.

COMMENTS

From the results of these experiments it becomes apparent that, provided adequate precautionary measures, including simultaneous controls and duplication of each experiment, are carried out, neither testosterone propionate nor estradiol benzoate exerts any effect on the incidence, extent, or rapidity of gangrene produced by ergotamine tartrate in the tail of adult male and female albino rats.

Marked variations in the incidence of gangrene occur in the control as well as the treated groups, which is evidence of the unreliability of the ergotamine method. Previous studies, in which a so-called "gangrenous dose" was determined by preliminary assays, so that the carrying out of simultaneous controls with each experiment was not deemed necessary, are certainly open to criticism. There is no doubt that this explains some of the more capricious conclusions.

A definite explanation cannot be offered for the variation in the dose of ergotamine tartrate required for the production of gangrene by the various investigators. It seems probable that preparations of different potencies must have been used. Variations in susceptibility to ergotamine poisoning between different strains of rats must be considered as a possibility. We obtained similar results, however, in two different strains of rats which were used in preliminary experiments. Perhaps inadequate nutrition might also account for differences in susceptibility. The rats in this study showed a rather high resistance against the ergotamine tartrate which we used. When considered in terms of a 70-kg. man, the daily dose of ergotamine tartrate required to produce gangrene would amount to 1,750 mg. This is of interest in regard to the increasing clinical use of ergotamine tartrate in the treatment of migraine, pruritus, and disturbances of the sympathetic nervous system.

Since the factors of strain, age of rats, nutrition, dosage, and technique of administration of ergotamine tartrate were not variable beyond narrow limits in our experiments, the differences in the incidence of gangrene in the control groups remain unexplained. The unreliability of the ergotamine method was also noted by Loewe and Lenke when a commercial preparation was used. Unfortunately, we were not able to obtain dry ergotamine powder, such as was used by these investigators to prepare fresh ergotamine tartrate solution on the day of the experiment. There are, however, indications that other factors which were variable in the successive experiments, such as surrounding temperature or seasonal influences, might be responsible for these variations.

Griffith and Comroe[9] presented experimental and clinical evidence that hyperthyroidism and peripheral vasodilatation are factors which facilitate the production of ergotamine gangrene. The stimulating effect of prolonged exposure to cold on the thyroid glands of rats is known through the work of Cramer,[10] and also of Starr and Roskelly.[11] On the other hand, peripheral vasodilatation produced in the tails of rats by a high surrounding temperature might perhaps also predispose to gangrene of the tail after ergotamine poisoning. Observations in this laboratory have shown that the skin temperature of the tails of rats very closely follows variations of the room temperature. Thus, it appears not unlikely that external factors, such as low and high surrounding temperatures, influence the tolerance of rats to ergotamine tartrate. Further studies on the influence of similar external factors on the production of ergotamine gangrene are suggested.

CONCLUSIONS

The administration of testosterone propionate or estradiol benzoate does not exert any influence on the incidence, extent, or rapidity of the gangrene produced by ergotamine tartrate in the tails of adult male and female albino rats.

REFERENCES

1. McGrath, E. J. G.: Experimental Peripheral Gangrene. Effect of Estrogenic Substance and Its Relation to Thrombo-Angiitis Obliterans, Arch. Int. Med. **55:** 942, 1935.
2. Herrmann, L. G., and McGrath, E. J. G.: Effect of Estrogene on Vascular Spasm Due to Active Angiitis in the Extremities, Arch. Surg. **40:** 334, 1940.
3. Suzmann, M. M., Freed, C. C., and Prag, J. J.: The Effect of Ovarian Follicular Hormone and of Castration on the Development of the Trophic Changes Produced by Ergotamine Tartrate in Albino Rats, South African J. M. Sc. **3:** 29, 1938.
4. Ratschow, M., and Klostermann, H. C.: Experimentelle Befunde zur Gefaesswirkung der Sexualhormone und ihre Beziehungen zur Klinik der peripheren Durchblutungsstoerungen, Ztschr. f. klin. Med. **135:** 198, 1938.
5. Cobet, R., Ratschow, M., and Steckner, M. L.: Experimentelle Untersuchungen über die Wirkung eines synthetischen Follikulinersatzstoffes Diäthyldioxystilben (Cyren) auf die periphere Blutversorgung, Klin. Wchnschr. **18:** 278, 1939.
6. Loewe, L., and Lenke, S. E.: The Use of Estrogenic Hormone in Experimental Peripheral Gangrene, J. Pharmacol. & Exper. Therap. **63:** 93, 1938.
7. Rothlin, E.: Recherches expérimentales sur l'ergotamine, alcaloide specifique de l'ergot de seigle, Arch. internat. de pharmacodyn. et de thérap. **27:** 459, 1923.
8. Thomas, R. M.: Sex Hormone Therapy in Experimental Peripheral Gangrene, Yale J. Biol. & Med. **12:** 415, 1940.
9. Griffith, J. Q., Jr., and Comroe, B. I.: Reduced Tolerance to Ergotamine Tartrate in Hyperthyroidism, J. Pharmacol. & Exper. Therap. **69:** 34, 1940.
10. Cramer, W.: Fever, Heat Regulation, Climate and the Thyroid Adrenal Apparatus, London, 1928, Longmans, Green & Co.
11. Starr, P., and Roskelly, R.: A Comparison of the Effects of Cold and Thyrotropic Hormone on the Thyroid Gland, Am. J. Physiol. **130:** 549, 1940.

RHEUMATIC CARDITIS IN A TROPICAL COUNTRY

E. García Carrillo, M.D.
San José, Costa Rica

THE epidemiology of rheumatic fever has been well covered,[1-3] but we wish to point out the influence of climatic conditions. The following data may prove useful for future reference.

Costa Rica is situated in Central America, and its capital, San José, lies more or less at 10° latitude North. This town occupies a healthy position on a narrow plateau, 25 miles long by 12 miles wide, whose altitude above sea level varies between 3,000 and 4,000 feet. The characteristic features of a tropical climate, somewhat influenced by the altitude, are present. The average humidity is 80 per cent, and the temperature is 19° C. (66° F.), with extremes ranging from 12° C. (54° F.) to 32° C. (90° F.). The average daily precipitation during the rainy months is 10 mm., that is, from June through November. The dry season ("verano") starts in December; it is influenced by northeast winds which bring dry and fresh weather. The average barometric pressure is 66.5 mm., with minimum oscillations. The sun shines most of the time.

In various towns around San José, rheumatic fever and chorea are known to be present, although the exact incidence cannot be ascertained at present because of lack of information from hospitals and various government agencies which we have consulted. In the period from April, 1936, to April, 1939, we found twenty-two cases of rheumatic fever, chorea, and endocarditis among 3,771 clinical records from the pediatric ward of the Hospital San Juan de Dios, at San José.[4] The diagnoses were made by different observers and were not checked by us. The diagnostic criteria of heart involvement were unsatisfactory, for no electrocardiograms were taken, and therefore it is possible that other cases escaped unnoticed. The incidence of mitral stenosis in the last 1,000 autopsies performed at the same hospital was 1.1 per cent (from April, 1939, to May, 1941). This figure is higher than the one given by Harrison and Levine[3] at the Charity Hospital in New Orleans.

This report covers some cases which were analyzed by clinical and laboratory methods (roentgenology, electrocardiography, sedimentation rate, etc.). They come from our own private practice in the last three years, but other cases in which we are unable to present the electrocardiographic record are omitted, including one patient who died with typical subacute bacterial endocarditis, superimposed on rheumatic lesions (Table I).

Received for publication May 27, 1941.

COMMENT

Various reports[1-3] have shown that rheumatic fever and carditis seem to be more common in the northern part of the United States than in its southern regions. Therefore, it has been concluded that, in order to prevent recurrences, rheumatic patients should go south. But what

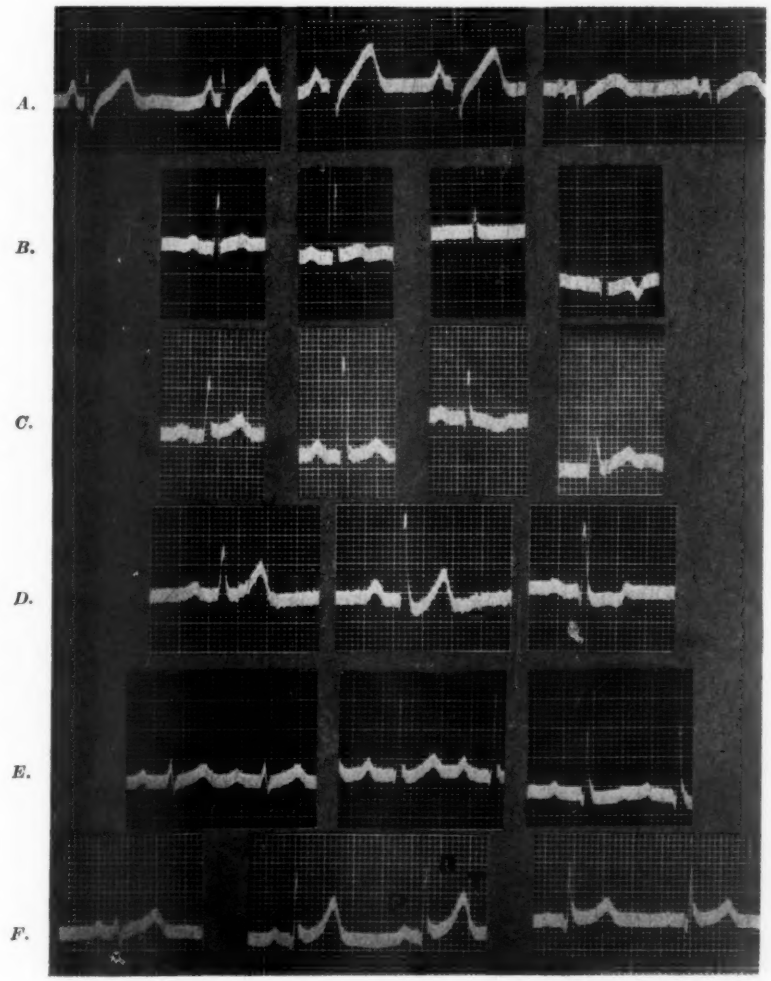

Fig. 1.

has been disregarded by most observers is the fact that, although this malady may occur less frequently, it has by no means been proved that it is less serious or that its course is not the same or at least delayed. Here we have cases occurring in a tropical climate, and, in the course of a few years, the patients develop multiple valvular lesions and die.

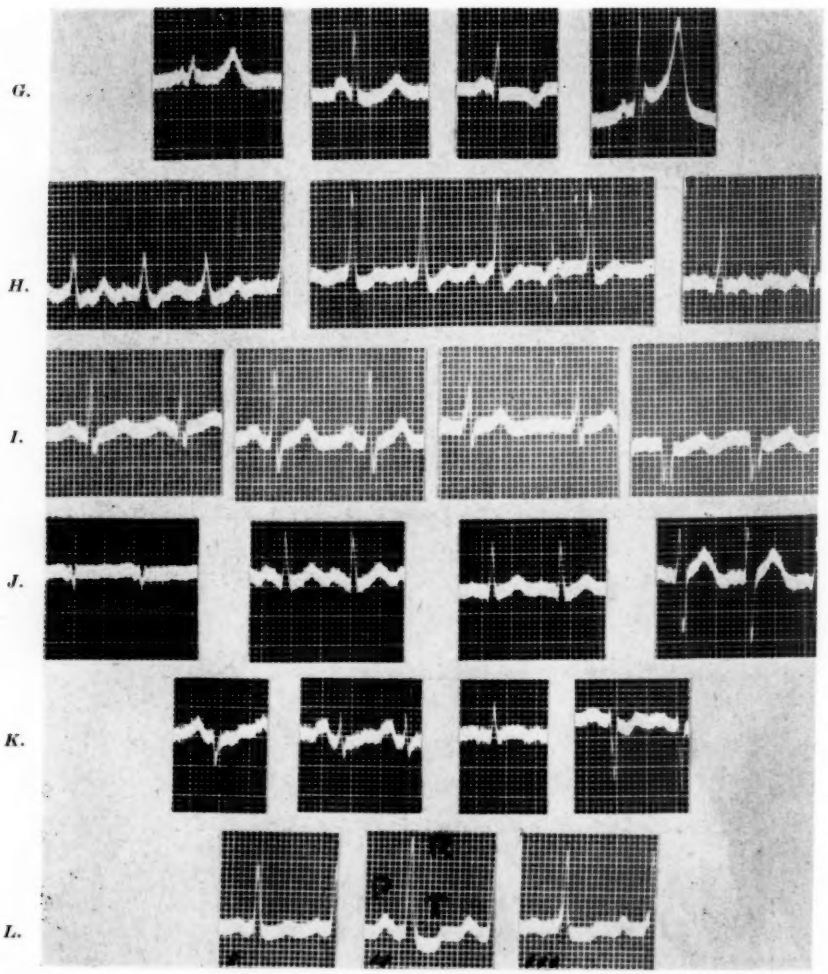

Fig. 2.

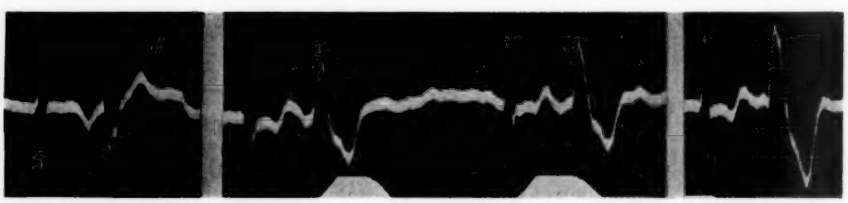

Fig. 3.—Electrocardiogram of a man, 18 years old, who died three years after the onset of rheumatic heart disease. It shows auricular fibrillation, complete A-V block, and left ventricular premature beats (bigeminy). Digitalis effect on RS-T segment; extreme R. V. preponderance.

In the study made by Jones and his associates,[5] caution has already been expressed with regard to the advisability of transportation to a subtropical climate.

It is evident that many factors may be concerned with the occurrence of the rheumatic infection in a given child or adolescent, but climate alone should not be given undue importance; other factors also play a role in determining the evolution and cardiac sequels.

TABLE I

AGE (YEARS)	SEX	CHRONOLOGICAL DEVELOPMENT OF THE DISEASE	ELECTROCARDIOGRAM
11	M	1938, rheumatic fever and chorea 1941, mitral valve disease	Fig. 1*A*, high amplitude of P waves (2.5 mm.)
22	M	1939, acute rheumatic pericarditis 1941, slight "rouff-ta-ta"	Fig. 1*B*, May, 1939 Fig. 1*C*, July, 1939 Fig. 1*D*, March, 1941, changing amplitude of P-R and T waves
17	M	1940, rheumatic fever and pericarditis 1941, no symptoms or signs	Fig. 1*E*, August, 1940 Fig. 1*F*, October, 1940, changing amplitude of waves and P-R segment (0.21-0.18)
31	M	1940, early (?) mitral valve disease	Fig. 2*G*, short P-R, notched P, and very high T_4 (15 mm.)
36	M	1911, chorea 1941, mitral and aortic valve disease	Fig. 2*H*, auricular fibrillation
14	M	1937, rheumatic fever 1941, mitral valve disease	Fig. 2*I*, notched P, measuring 0.10 sec.; notched R_3
10	F	1939, undetermined fever 1941, mitral and aortic valve disease; unknown cause of death	Fig. 2*J*, notched P, measuring 0.12 sec.; flat T_1; definite R.V. preponderance
25	F	1923, 1934, 1938, rheumatic fever 1941, mitral and aortic valve disease; unknown cause of death	Fig. 2*K*, plateau P_2; diphasic or isoelectric T; tendency to low R; extreme R.V. preponderance
30	F	1924, rheumatic fever 1940, mitral and aortic valve disease 1941, acute, fatal serosanguineous pericarditis	Fig. 2*L*, notched P_2, measuring 0.12 sec.; digitalis effect on RS-T segment
18	M	1936, "palpitations" 1938, rheumatic panvalvulitis 1939, fatal congestive heart failure	See Fig. 3

SUMMARY

We have tried to show that living in a tropical country by no means constitutes a safeguard against rheumatic infection or the development of severe rheumatic carditis. We present data from our own practice and from the Hospital San Juan de Dios.

REFERENCES

1. Paul, J. R.: The Epidemiology of Rheumatic Fever (in Stroud, W. D.: The Diagnosis and Treatment of Cardiovascular Disease,'' Philadelphia, 1940, Davis, Vol. I, p. 84).
2. Swift, H. F.: Public Health Aspects of Rheumatic Heart Disease, J. A. M. A. **115:** 1509, 1940.
3. White, P. D.: Heart Disease, New York, 1937, Macmillan Co., p. 233.
4. Carrillo, E. García: Observations on the Incidence of Rheumatic Fever in Costa Rica. Report to the VIII American Scientific Congress, Washington, D. C., May, 1940.
5. Jones, T. D., White, P. D., Roche, C. F., Perdue, J. J., and Ryan, H. A.: The Transportation of Rheumatic Patients to a Subtropical Climate, J. A. M. A. **109:** 1308, 1937.

THE PERIPHERAL BLOOD FLOW IN MYXEDEMA AS COMPARED WITH THAT IN HYPERTHYROIDISM

HAROLD J. STEWART, M.D., AND WILLIS F. EVANS, M.D.*
NEW YORK, N. Y.

THE cardiac output,[1] the circulating blood volume,[2] the velocity of blood flow, the pulse rate, the pulse pressure, and the vital capacity[3] are decreased when the basal metabolism[4] is low in myxedema. The pale, cold, dry skin of patients suffering from this disease suggested that there might be alterations of peripheral blood flow. Objective measurements, however, are not in the literature relating to the amount of blood allocated to the periphery. Stewart and Evans[5] found that the peripheral blood flow in hyperthyroidism was increased and that it decreased with the administration of iodine and further still after subtotal thyroidectomy, so that there was a linear relationship between basal metabolic rate and peripheral blood flow. In these patients the increase in peripheral blood flow accounted for the pink, moist skin which they exhibited. It was of interest, therefore, to measure the peripheral blood flow in myxedema, which is at the other end of the metabolic scale from hyperthyroidism. These data have now been accumulated and compared with measurements on patients with hyperthyroidism.[5]

Six women suffering from myxedema were observed. Four of them suffered from spontaneous myxedema (E. S., L. C., M. P., and R. M., Table I) and two, from postoperative myxedema (M. K., and E. B., Table I). Data on six female hyperthyroid patients (C. DiP., M. H., E. B., K. H., N. L., and A. S.), on whom measurements of peripheral blood flow had been made at the same environmental temperatures which prevailed at the time the myxedema patients were observed, were chosen for comparison (Table II).[5] All subjects in both groups had normal sinus mechanism and no signs or symptoms of congestive heart failure.

METHODS

Measurements of peripheral blood flow were made with techniques similar to those used in other studies of the peripheral blood flow by Stewart and Jack[6] and Stewart and Evans.[5] In order to use this method, certain data were required, namely, recordings of skin temperature, for which a Hardy radiometer was used,

From the New York Hospital and the Department of Medicine, Cornell University Medical College, New York City.
Read before the Peripheral Vascular Section of the American Heart Association, May 31, 1941, Hotel Statler, Cleveland, Ohio.
Received for publication June 19, 1941.
*Lewis Cass Ledyard Fellow in Medicine, 1940-1941.

of rectal temperature, of oxygen consumption, of height, and of body weight. In addition, the blood pressure, the pulse rate, and the arm-to-tongue circulation time (decholin[7]) were recorded.

PLAN OF OBSERVATIONS

The order in which data were recorded was the same as that used in the observations on the patients with hyperthyroidism.[5] Six sets of skin and rectal temperatures, made at twenty-minute intervals, appeared to be sufficient. From these recordings, five average periods of peripheral blood flow were calculated.[5] The blood pressures and pulse rates were recorded during free intervals between temperature readings. The arm-to-tongue circulation time was measured after the last estimate of oxygen consumption. Observations subsequent to the initial phase were made in exactly the same sequence on each patient, and care was taken to reproduce the same environmental temperature.[5] Observations were made before treatment was instituted, and again on several occasions after the administration of thyroid extract, until the basal metabolic rate approached normal.

RESULTS

Metabolic Rate and Peripheral Blood Flow.—Before treatment, when the basal metabolic rate was low, the peripheral blood flow was also decreased. With progressive elevation of the basal metabolic rate to normal during the administration of thyroid extract, successive increases in peripheral blood flow occurred (Tables I and II) (Fig. 1).

Skin Temperature.—The average skin temperature was decreased at first and increased with the administration of thyroid extract. The average temperature of the hands and feet showed similar trends for the whole group (Tables I and II).

Rectal Temperature.—Changes in rectal temperature did not follow any pattern (Tables I and II).

Pulse Rate and Pulse Pressure.—The pulse rates of each of the six patients and in the group averages showed trends parallel with changes in basal metabolic rate and peripheral blood flow, that is to say, they increased with the giving of thyroid extract. The average pulse pressure also rose, except in one patient (E. B.) (Tables I and II).

Circulation Time.—The circulation time was prolonged before treatment. It became shorter during treatment with thyroid extract (Tables I and II) (Fig. 1).

DISCUSSION

These observations show that, at a time when the basal metabolic rate was low in the myxedematous subjects, the peripheral blood flow was also decreased. During the progressive rise in basal metabolic rate with the administration of thyroid extract there were successive and parallel increases in peripheral blood flow (Tables I and II) (Fig. 1). This relationship between peripheral blood flow and basal metabolic rate was linear (Fig. 2). On the other hand, Stewart and Evans[5] found that, during thyrotoxicosis, when the basal metabolic rate was

TABLE I

DATA RELATING TO SIX PATIENTS WITH MYXEDEMA

HISTORY NO.	NAME	AGE (YR.)	SEX	DIAGNOSIS	DATE	HEIGHT (CM.)	WEIGHT (KG.)	TOTAL SURFACE AREA (SQ.M.)	TOTAL HEAT PRODUCTION* (CAL./HR.)	AV. ROOM TEMP. (° C.)	AV. RECTAL TEMP. (° C.)	AV. SKIN TEMP.† (° C.)	AV. HAND TEMP. (° C.)	AV. FOOT TEMP. (° C.)	BASAL METABOLIC RATE (%)	PERIPHERAL BLOOD FLOW (C.C./M²/MIN.)	CIRCULATION TIME (DECHOLIN) (SEC.)	PULSE RATE (PER MIN.)	PULSE PRESSURE (MM. HG)	THYROID EXTRACT THERAPY (GM. DAILY)
256220	L. C.	60	F	Spontaneous myxedema	2/ 6/40	155.5	78.0	1.78	41.2	27.6	36.79	33.76	33.2	32.2	–30	14	14.9	60	22	None
					3/ 2/40	155.5	76.5	1.77	47.1	27.5	36.96	33.78	34.3	33.8	–18	49	12.8	73	34	0.012
					3/30/40	155.5	71.8	1.72	65.2	27.7	37.46	34.61	34.4	35.1	+16	137	11.5	90	30	0.060
					1/10/41	155.5	71.7	1.72	52.6	27.5	36.82	34.17	34.2	33.8	– 4	91	11.2	74	54	0.075
258799	E. S.	32	F	Spontaneous myxedema	2/13/40	167.5	63.1	1.71	40.1	25.6	37.31	33.10	32.3	26.9	–34	22	21.8	49	20	None
					4/ 5/40	167.5	63.4	1.71	43.4	25.8	37.19	33.89	34.6	31.6	–29	61	20.1	48	30	0.045
					5/14/40	167.5	61.7	1.70	48.6	26.1	37.41	33.83	35.1	32.6	–19	71	12.5	59	36	0.120
					1/13/41	167.5	59.4	1.69	62.5	25.9	36.74	32.72	32.7	28.0	+ 5	92	10.9	60	34	0.210
145380	M. P.	30	F	Spontaneous myxedema	1/ 6/41	170.0	63.4	1.74	49.8	26.0	36.91	33.24	28.8	31.4	–20	10	12.9	60	24	None
					3/29/41	170.0	61.1	1.72	58.8	26.2	36.92	33.80	29.8	32.5	– 6	78	12.2	68	36	0.060
					4/19/41	170.0	60.8	1.71	60.0	26.0	36.56	33.18	32.9	33.1	– 2	79	12.3	64	32	0.120
271344	R. M.	30	F	Spontaneous myxedema	11/ 7/40	161.5	85.8	1.91	50.8	25.0	36.86	31.74	31.7	27.5	–26	7	19.6	60	12	0.015
					1/11/41	161.5	84.1	1.88	58.6	25.2	36.74	33.12	33.5	32.2	–13	55	16.6	64	26	0.030
					4/26/41	161.5	85.1	1.89	67.6	25.1	37.23	33.58	33.2	32.6	0	90	15.0	64	24	0.120
196749	M. K.	39	F	Postoperative myxedema	11/ 6/40	147.0	66.8	1.60	32.8	25.2	36.87	32.19	31.1	27.2	–43	33	17.0	60	20	None
					1/ 2/41	147.0	66.7	1.60	53.4	25.5	37.34	34.14	34.4	29.8	– 7	68	14.9	66	30	0.030
					2/14/41	147.0	68.3	1.61	58.6	25.1	36.86	33.97	34.0	30.3	+ 2	87	12.4	64	30	0.150
170489	E. B.	42	F	Postoperative myxedema	1/16/41	172.0	67.4	1.82	43.7	25.0	36.90	32.96	31.2	23.5	–33	9	19.5	68	66	None
					2/ 3/41	172.0	67.0	1.83	62.7	25.2	37.25	34.21	35.2	26.4	– 7	71	15.1	72	50	0.060
					3/ 4/41	172.0	67.5	1.83	68.0	25.3	37.28	34.29	34.2	31.9	– 3	81	14.0	68	46	0.150

*Calculated from oxygen consumption.[5]

†Calculated from weighting the eleven individual skin temperatures according to the surface area represented by each.[5]

high the peripheral blood flow was increased. Parallel decreases in basal metabolic rate and peripheral blood flow occurred during iodine therapy, and both returned to normal levels after subtotal thyroidectomy (Table II).[5] The linear relationship between basal metabolic rate and peripheral blood flow in these two diseases is shown when data on all patients are plotted on the same chart (Fig. 2). With progressive increases from the low basal metabolic level of the myxedematous state to the high basal metabolic level of the hyperthyroid subjects, there was a progressive increase in the peripheral blood flow. The intercepts with the zero line were, however, slightly different (Fig. 2). The scattering of peripheral blood flow at various levels for individual patients was interpreted as due, in part, to different basal metabolic rates, and, in part, to different room temperatures for each patient (Fig. 1). Hick, Keeton, Glickman, and Wall[8] and Hardy and Soderstrom[9] have shown that there is a correlation between rise in environmental temperature and increase in peripheral blood flow. Observations published recently by Stewart and Evans[5] are in agreement with these findings. For this reason, care was exercised to keep environmental temperature approximately the same during all observations on any one patient.

TABLE II

AVERAGES OF MEASUREMENTS ON SIX PATIENTS WITH HYPERTHYROIDISM FOR COMPARISON WITH THOSE ON SIX PATIENTS SUFFERING FROM MYXEDEMA

	BASAL METABOLIC RATE (%)	PERIPHERAL BLOOD FLOW (C.C./M²/MIN.)	CIRCULATION TIME (SEC.)	PULSE PRESSURE (MM. HG)	PULSE RATE (PER MIN.)	AV. SKIN TEMP. (° C.)	RECTAL TEMP. (° C.)	HAND TEMP. (° C.)	FOOT TEMP. (° C.)
Hyperthyroidism									
Before iodine	+45	210	8.4	55	106	34.63	37.28	35.2	33.0
During iodine	+24	139	10.6	45	80	34.39	37.19	34.9	31.8
After operation	+ 8	68	13.6	39	72	33.66	37.21	34.6	29.9
Myxedema									
Before treatment	−29	16	17.6	27	60	32.83	36.94	31.4	28.1
During thyroid extract	−12	65	14.1	35	69	33.81	37.10	33.7	31.2
During thyroid extract	− 2	87	12.6	37	66	33.65	36.92	33.5	33.3

Before treatment, when the basal metabolic rate and peripheral blood flow were low, the average skin temperature was also decreased. Increases in average skin temperature occurred during the administration of thyroid extract.

In the subjects with hyperthyroidism, on the other hand, there was an elevation of average skin temperature before treatment, with a progressive decrease to normal levels during iodine therapy and after operation. In short, treatment of the myxedematous patients with

thyroid extract raised average skin temperature to normal levels, and iodine therapy and subtotal thyroidectomy in the case of the thyrotoxic patients decreased it to normal levels (Table II).

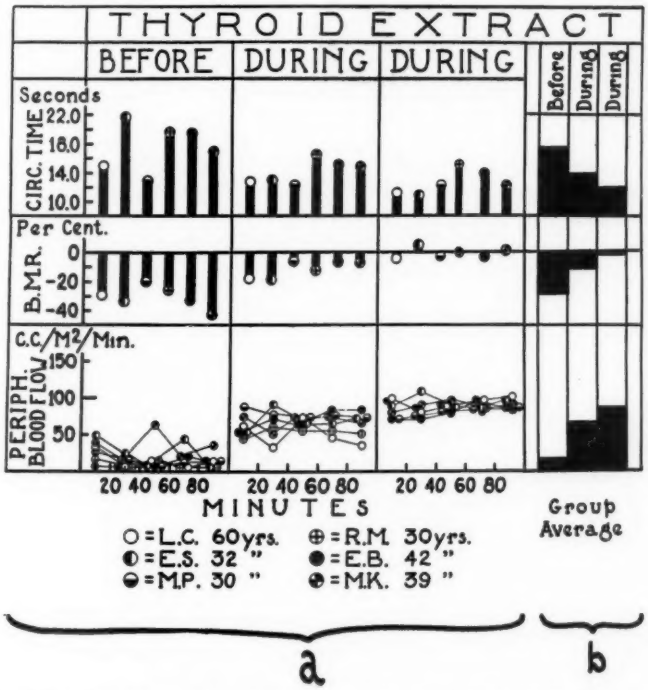

Fig. 1.—Peripheral blood flow, basal metabolic rate, and circulation time of six patients suffering from myxedema, before and during the administration of thyroid extract (Fig. 1*a*). Each patient is represented by a symbol. In Fig. 1*b*, averages for the data on the six patients are shown.

The recent studies on hyperthyroidism[5] showed no direct relationship between the temperature of the hands and feet and average skin temperature. This was the case also in myxedematous patients. In myxedema the average temperature of the hands followed average skin temperature more closely, whereas the average temperature of the feet more nearly paralleled the changes in peripheral blood flow and basal metabolic rate. The data on L. C. (Table I) (Fig. 3) are presented in detail to bring out these points.

The change in rectal temperature in each case, as well as the average rectal temperature of all patients in the myxedema group and in the hyperthyroid group, was much less marked than the alteration in average skin temperature (Tables I and II).[5] This emphasizes a point brought out by Burton,[10] namely, that, although rectal temperature has the larger weighting coefficient, surface (average skin) temperature is the more important because it changes more in short periods.

Stewart, Deitrick, and Crane[1] found that the cardiac output was low in myxedema and increased to normal with the rise in basal metabolic

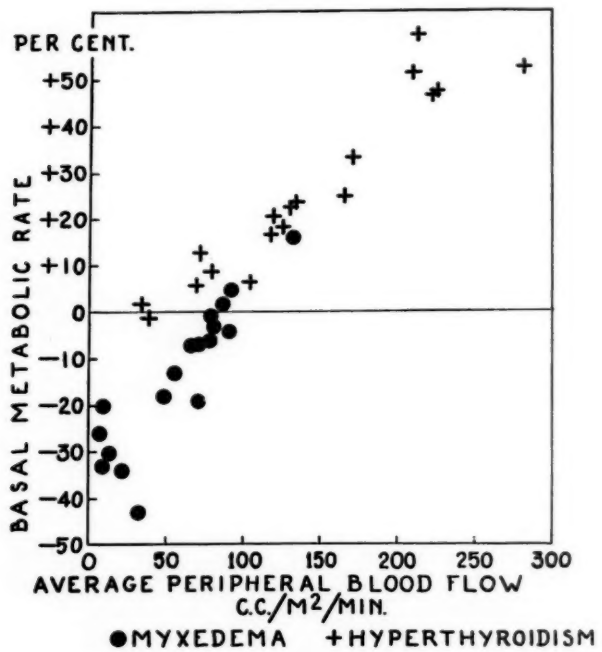

Fig. 2.—The data for the peripheral blood flow of the myxedema patients (Table I) (Fig. 1) and of six hyperthyroid patients (Stewart and Evans[5]) are plotted against corresponding basal metabolic rates. A linear relationship is established, for, with the increase in basal metabolic rate from the low level of myxedema to the high level of thyrotoxicosis, the peripheral blood flow also increased.

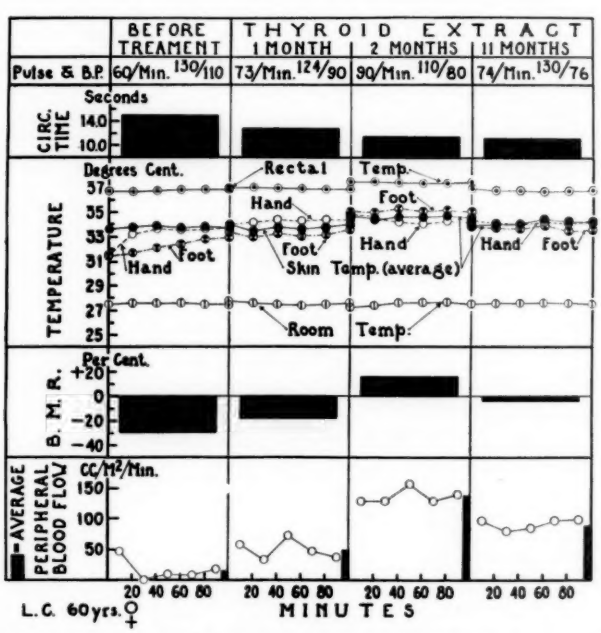

Fig. 3.—Data relating to subject L. C., who was suffering from myxedema.

rate caused by administration of thyroid extract. The average cardiac output in the group they reported, at basal metabolic rates comparable to those at which these studies of peripheral blood flow were made, is shown in Fig. 4. The allotment of the cardiac output to the various organs in man is not known. In myxedema, when the cardiac output is low, the amount allotted to the skin is now found to be decreased. At the average basal metabolic rate of –30 per cent, about 1.3 per cent of the cardiac output was allotted to the skin. On the return of cardiac output to normal during thyroid extract therapy, the peripheral blood flow increased also, so that approximately 4 per cent of the output was now allotted to the skin.

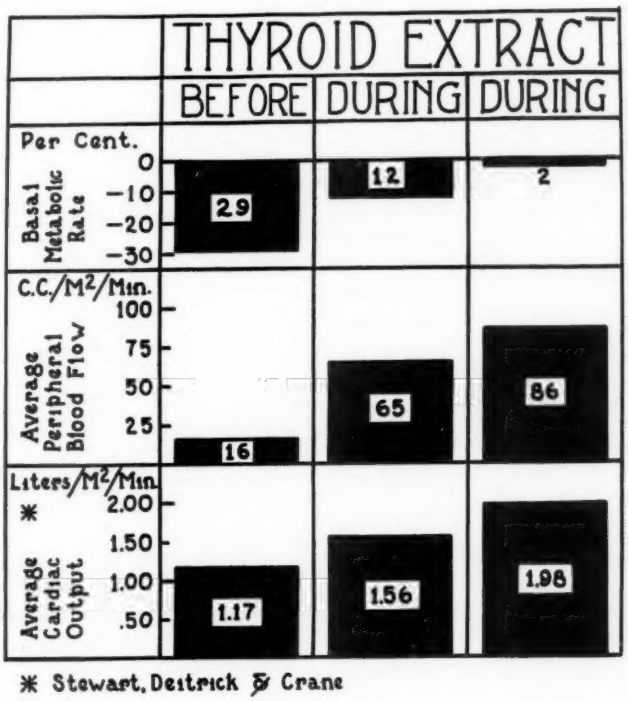

Fig. 4.—The average basal metabolic rate and the average peripheral blood flow of the six myxedema patients, together with the average cardiac output of myxedematous patients, at comparable levels of basal metabolism, taken from the data of Stewart, Deitrick, and Crane.[1]

The cardiac output is increased in thyrotoxicosis[11] and decreases with the administration of iodine and again after subtotal thyroidectomy. Stewart and Evans[5] measured the cardiac output in one patient, A. S. (History No. 230995), who was suffering from hyperthyroidism, in order to correlate it with the peripheral blood flow. The procedure was exactly the same as that followed by one of us on another occasion.[1] Before giving iodine, at a time when the basal metabolic rate was +60 per cent, there was an allotment of 6 per cent of the

cardiac output to the peripheral circulation. During iodine therapy, and again after operation, when the basal metabolic rates were +18 and +6 per cent, respectively, the amounts of blood allocated to the periphery were 5 and 3 per cent, respectively, of the volume output of the heart.[5]

From Stewart, Deitrick, and Crane's observations,[1] it appeared that the cardiac output per minute and per beat was decreased to such an extent in the myxedematous state that, in order to maintain an adequate circulation even for the lowered metabolic requirements of the organism, an increase in the arteriovenous oxygen difference took place. The observations now being reported demonstrate that the amount of blood allotted to the periphery was small when the patients were suffering from myxedema (Fig. 4). Increased blood flow to the surface indicates increased heat loss. These data suggest that the mechanism responsible for the circulatory phenomena of thyroid insufficiency acts to conserve heat, for not only was the total cardiac output and that portion allocated to the body surface decreased, but the velocity of blood flow was so slow that the arteriovenous oxygen difference was increased. Boothby and Rynearson[11] observed that, in thyrotoxicosis, there was a greater increase in cardiac output than occurred in normal subjects as a result of a corresponding increase in oxygen consumption due to work. It was shown that during this time the arteriovenous oxygen difference was decreased. Recent observations of Stewart and Evans[5] showed a marked increase in peripheral blood flow during the hyperthyroid state. Since the total cardiac output and peripheral blood flow were greater than those required for tissue metabolism (decreased arteriovenous oxygen difference), the increased peripheral blood flow in thyrotoxicosis served to increase heat loss, whereas the decreased peripheral blood flow in myxedema served to conserve heat.

In these studies, as in those on hyperthyroidism,[5] the circulation time was estimated in order to have an additional objective measurement to correlate with peripheral blood flow. The results demonstrate that, in the myxedematous state, when the basal metabolic rate and peripheral blood flow were decreased, the circulation time was prolonged. With a progressive increase in the former during the administration of thyroid extract, there was a progressive decrease in circulation time (Tables I and II) (Fig. 1). These results were the reverse of those found in cases of hyperthyroidism (Table II).[5]

SUMMARY

A method described in previous papers[5, 6] was used. Measurements were made of peripheral blood flow in six patients suffering from myxedema and were compared with similar observations of Stewart and Evans[5] on six subjects who had hyperthyroidism. The myxedematous subjects were studied before treatment and on several occasions during

the course of administration of thyroid extract. In addition, certain other measurements of the circulation were recorded. The results may be summarized as follows:

1. In the myxedematous state, when the basal metabolic rate was low, the peripheral blood flow in cubic centimeters per square meter per minute was decreased. With a progressive increase in basal metabolic rate to normal levels during the administration of thyroid extract there was a progressive increase in peripheral blood flow, so that a linear relationship was maintained. On the other hand, as the basal metabolic rate decreased with therapy in the thyrotoxic subjects, there was a progressive decrease in peripheral blood flow; here again, a linear relationship was present. When the peripheral blood flow of the patients of both groups was plotted against basal metabolic rate, the line for the myxedema patients was a rough continuation of the hyperthyroid one; the intercepts with the zero line, however, were slightly different.

2. Since there is a decrease in cardiac output in myxedema and an increase in hyperthyroidism, a smaller than normal amount of blood appears to be available for distribution to the skin in the myxedema patient, and a greater amount in the hyperthyroid one.

3. The circulation time was prolonged in myxedema and short in thyrotoxicosis. When appropriate treatment was instituted, the circulation time returned to normal in each disease.

4. In myxedema the pulse rate and pulse pressure followed roughly the increases in basal metabolic rate and peripheral blood flow. In subjects with hyperthyroidism the fall in pulse rate and pulse pressure roughly paralleled decreases in basal metabolic rate and peripheral blood flow.

5. For the most part, average skin temperature followed the changes in basal metabolic rate and peripheral blood flow in each disease. Similar trends were observed in the temperature of the hands and feet. No direct relationship was established, however, between average skin temperature and the temperature of the hands and feet.

6. No constant or significant changes in rectal temperature were observed in either disease during the several periods of study of each subject.

7. Conservation of heat in myxedema and increased heat dissipation in thyrotoxicosis have been suggested as an explanation for the marked decrease in peripheral blood flow in the former and its increase in the latter.

REFERENCES

1. Stewart, H. J., Deitrick, J. E., and Crane, N. F.: Studies of the Circulation in Patients Suffering From Spontaneous Myxedema, J. Clin. Investigation **17**: 247, 1938.
2. Gibson, J. G., II, and Harris, A. W.: Clinical Studies of the Blood Volume. II. Hyperthyroidism and Myxedema, J. Clin. Investigation **18**: 65, 1939.

3. Blumgart, H. L., Gargill, S. L., and Gilligan, D. R.: Studies in Velocity of Blood Flow. XIV. The Circulation in Myxedema With a Comparison of the Velocity of Blood Flow in Myxedema and Thyrotoxicosis, J. Clin. Investigation **9**: 91, 1931.
4. Du Bois, E. F.: Basal Metabolism in Health and Disease, Philadelphia, 1936, Lea & Febiger, p. 318.
5. Stewart, H. J., and Evans, W. F.: The Peripheral Blood Flow in Hyperthyroidism, AM. HEART J. **20**: 715, 1940.
6. Stewart, H. J., and Jack, N. B.: The Effect of Aminophyllin on Peripheral Blood Flow, AM. HEART J. **20**: 205, 1940.
7. Tarr, L., Oppenheimer, B. S., and Sager, R. W.: The Circulation Time in Various Clinical Conditions Determined by the Use of Sodium Dehydrocholate, AM. HEART J. **8**: 766, 1933.
8. Hick, F. K., Keeton, R. W., Glickman, N., and Wall, H. C.: Cardiac Output, Peripheral Blood Flow and Blood Volume Changes in Normal Individuals Subjected to Varying Environmental Temperatures, Heating, Piping and Air Conditioning, p. 50, January, 1939.
9. Hardy, J. D., and Soderstrom, G. F.: Heat Loss From the Nude Body and Peripheral Blood Flow at Temperature of 22° C. to 35° C., J. Nutrition **16**: 439, 1938.
10. Burton, A. C.: Human Calorimetry. II. The Average Temperature of the Tissues of the Body, J. Nutrition **9**: 261, 1935.
11. Boothby, W. M., and Rynearson, E. H.: Increase in Circulation Rate Produced by Exophthalmic Goiter Compared With That Produced in Normal Subjects by Work, Arch. Int. Med. **55**: 547, 1935.

DISCUSSION

DR. WILLIS F. EVANS, New York, N. Y.—There is nothing further that I have to add, except that I should like to comment briefly on heat conservation in myxedema and heat dissipation in hyperthyroidism—points which the allotted time this afternoon would not permit.

During thyroid insufficiency the cardiac output is low, and the studies just reported show that the amount of blood allotted to the periphery is small (about 1 per cent before treatment and approximately 4 per cent after giving adequate amounts of thyroid extract). In addition, the arteriovenous oxygen difference is increased, and the velocity of blood flow is decreased in this disease. These data suggest that the mechanism responsible for the circulatory changes in myxedema conserves heat, for not only are the total cardiac output and that portion allotted to the periphery decreased, but the velocity of blood flow is so slow that, in order to maintain an adequate circulation even for the lowered metabolic requirements of the organism, an increase in the arteriovenous oxygen difference takes place.

Graves' disease stands at the opposite end of the metabolic scale. We have made measurements of the cardiac output and peripheral blood flow in one patient suffering from Graves' disease. We found that before treatment the amount of blood allotted to the periphery was approximately 6 per cent of the total cardiac output, whereas, after subtotal thyroidectomy, the allotment was only 3 per cent of the cardiac output. The cardiac output in Graves' disease is increased above the metabolic requirements of the tissues. This has been demonstrated by Boothby and Rynearson, who attributed this change to some sympathetico-stimulating substance circulating in the blood. Moreover, the arteriovenous oxygen difference is *decreased* in thyrotoxicosis at a time when the cardiac output is increased out of proportion to the basal metabolic rate. Increased blood flow to the surface brings about increased heat loss, and it is to this end that the circulation appears to be changed in thyrotoxicosis, for in this disease the total cardiac output and peripheral blood flow are greater than is required for tissue metabolism, as indicated by a decreased arteriovenous oxygen difference.

A STUDY OF THE RATE OF WATER LOSS FROM THE SURFACES OF THE FINGER TIPS AND TOE TIPS OF NORMAL AND SENILE SUBJECTS AND PATIENTS WITH ARTERIAL HYPERTENSION

G. E. Burch,* M.D., A. E. Cohn, M.D., and C. Neumann, M.D.
New York, N. Y.

THE role of the sympathetic nervous system in the pathogenesis of arterial hypertension has not been adequately defined. There is evidence to show that there may be an increase in sympathetic tone.[1, 2] Most of these observations have been limited to the influence of the sympathetic nervous system on the cardiovascular system. The degree of sympathetic activity, especially in patients with arterial hypertension, may be estimated by measuring the rate of water loss from the skin. Such studies seem not to have been undertaken. It has been widely observed that resting and apparently comfortable patients with hypertension have cold and clammy extremities and that cutting certain sympathetic nerves leads to dryness of the extremities, but this has been observed likewise in other people. It was thought that quantitative measurements of the rate of sweating in normal and senile subjects and in patients with hypertension might throw light on the role of the sympathetic nervous system, and these investigations were therefore undertaken.

METHOD

The method used in these studies has already been described.[3] It consists essentially of passing dry oxygen through chambers covering the skin of fingers and toes, and then conducting the moisture-laden oxygen through cold coils. From the difference in weight of the coils before and after the passage of oxygen, the amount of water lost is learned. First, the subjects rested for thirty minutes in a special room[4] (temperature 75° F. ±1°, relative humidity less than 50 per cent). This room was designed to remove all the appearances of a laboratory. The subjects were alone and undisturbed throughout the periods of observation; collections of sweat, weighing, and other manipulations were carried out in an adjoining room, separated from the subject's room by a sound-proof wall. The collections were made continuously for sixty minutes at fifteen-minute intervals. These observations were made during the last week of March, April, and the first two weeks of May, 1941.

From the Hospital of the Rockefeller Institute for Medical Research, New York.
This is the fourth paper reporting the results of studies of the small blood vessels and related subjects.
Read before the Vascular Section, American Heart Association, Cleveland, May 30, 1941.
Received for publication June 23, 1941.
*Commonwealth Fund Fellow.

There were thirteen normal subjects whose ages ranged from 8 to 44 years, ten patients with arterial hypertension who were free from renal or cardiac failure and were between 27 and 54 years of age, and eight senile subjects who were free from renal or cardiac failure and were normal except for the usual manifestations of senility. The ages of the senile subjects varied from 70 to 85 years. In addition, a miscellaneous group was studied. These observations included measurements on two subjects with hypertension which were made before, and three weeks after, bilateral sympathectomy (ninth thoracic sympathetic nerve to first lumbar, and the celiac and aortic renal plexuses), on a subject with advanced Raynaud's disease and scleroderma, and on a normal subject, continuously, for a period of 12.25 hours, and also simultaneous measurements on four groups of two subjects each, in separate beds in the same room.

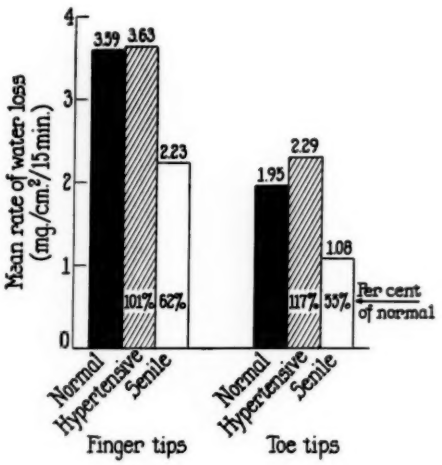

Fig. 1.—Mean rates of sweating of the tip of the right index finger and right second toe of groups of resting normal, hypertensive, and senile subjects.

The measurements were made simultaneously on the tip of the right index finger and right second toe of all subjects. In some instances it was the left index finger or left second toe (or both) that was examined simultaneously with the right ones. The areas of the finger and the toe nails were subtracted from the respective total areas of the parts examined, so that the results apply to the effective area only. The total areas were measured as previously described,[3] and the areas of the nails, by measuring the area of paper necessary to cover the nails of the positive casts of the parts. The temperature of the oxygen surrounding the parts in the chambers was 75° F., and the relative humidity, approximately zero. The temperature of the air surrounding the adjacent parts was 75° F., and the relative humidity, 50 per cent. In order to ascertain the influence of the dry oxygen on the rate of water loss from the parts enclosed in the chambers, observations were conducted in which room air and dry oxygen were used alternately to collect the water given off by the enclosed parts. It was found that the rate of water loss was the same whether the relative humidity was approximately zero or near 50 per cent.

RESULTS

The mean rate of water loss from the tips of the index fingers of the normal subjects was 3.59 mg. per square centimeter per fifteen minutes; the minimum and maximum variations were 1.84 and 6.96, respectively.

TABLE I

RATE OF SWEATING (MG./SQ. CM. SKIN AREA/15 MIN.) MEASURED SIMULTANEOUSLY ON THE RIGHT INDEX FINGER AND RIGHT SECOND TOE TIP OF 13 NORMAL, WHITE, RESTING ADULTS

SUBJECT NO.	DATE	AGE (YEARS)	SEX	BLOOD PRESSURE (MM. HG)	AREA OF SKIN (SQ. CM.)	FIRST 15 MIN.	SECOND 15 MIN.	THIRD 15 MIN.	FOURTH 15 MIN.	MEAN 15 MIN.	RATE OF SWEATING AS % OF FINGER RATE
					Finger Tips						
1	4/30/41	31	M	135/72	10.13	4.63	3.64	2.89	6.50	4.42	
2	3/28/41	41	M	120/70	11.22	2.48	3.23	2.91	2.78	2.85	
3	4/ 1/41	33	M	125/75	10.23	2.48	2.13	2.09	1.87	2.15	
6	5/ 3/41	40	F	110/70	8.64	2.56	2.31	4.23	4.21	3.35	
14	5/ 7/41	23	F	110/78	7.56	4.03	3.66	2.76	2.74	3.30	
24	5/ 1/41	29	F	110/80	7.56	2.39	4.72	5.22	6.42	4.69	
31	5/15/41	18	M	125/60	8.85	4.31	5.88	5.10	6.96	5.56	
49	5/13/41	26	F	110/65	8.66	5.57	4.50	3.46	2.75	4.07	
54	5/ 2/41	27	F	110/76	9.08	5.81	5.30	5.15	5.59	5.47	
66	5/ 5/41	37	M	115/75	10.76		3.04	2.36	2.10	2.50	
86	5/ 7/41	23	F	110/70	7.62	3.33	2.93	2.23	1.84	2.58	
92	5/ 1/41	44	M	118/78	10.26	2.45	2.63	2.36		2.48	
96	5/ 1/41	23	F	110/80	6.90	3.25	3.42	2.22	1.93	2.70	
Mean						3.61	3.65	3.31	3.81	3.59	
Maximum										6.96	
Minimum										1.84	
					Toe Tips						
1					8.10	2.00	1.55	2.03	1.70	1.85	42
2					8.22	1.92	1.72	1.38	1.12	1.54	54
3					9.05	1.98	1.81	1.72	1.78	1.82	85
6					8.60	1.24	1.18	1.64	1.51	1.40	42
14					7.98	1.56	1.04	1.13	1.17	1.23	56
24					8.22	1.13	1.60	2.12	3.07	1.98	42
31					9.66	2.93	3.74	2.84	2.81	3.08	55
49					8.44	2.71	2.30	1.67	1.34	2.00	49
54					8.29	6.81	4.92	4.38	3.84	4.99	91
66					8.67	1.34	1.20	1.12	0.96	1.15	46
86					7.96	1.62	1.34	0.72	0.67	1.09	42
92					8.69	1.45	1.27	1.40		1.37	55
96					6.84	2.30	2.38	1.17	1.33	1.79	66
Mean						2.23	2.00	1.79	1.78	1.95	54
Maximum										6.81	
Minimum										0.67	

TABLE II

RATE OF SWEATING (MG./SQ. CM. SKIN AREA/15 MIN.) MEASURED SIMULTANEOUSLY ON THE RIGHT INDEX FINGER TIP AND RIGHT SECOND TOE TIP OF 10 WHITE, RESTING ADULTS WITH ESSENTIAL HYPERTENSION

SUBJECT NO.	DATE	AGE (YEARS)	SEX	BLOOD PRESSURE (MM. HG)	AREA OF SKIN (SQ. CM.)	FIRST 15 MIN.	SECOND 15 MIN.	THIRD 15 MIN	FOURTH 15 MIN.	MEAN 15 MIN.	RATE OF SWEATING AS % OF FINGER RATE
Finger Tips											
28	3/21/41	29	F	245/145	8.33	3.78	5.20	4.35	3.31	4.16	
37	4/ 3/41	37	M	230/130	10.73	4.40	8.70	8.01	8.80	7.48	
40	3/26/41	38	F	220/148	9.31	1.84	1.99	1.98	1.92	1.93	
44	3/27/41	43	M	198/140	14.49	3.04	2.53	2.12	1.75	2.36	
58	3/26/41	27	F	242/130	8.67	4.81	3.56	4.65	3.71	4.19	
70	3/24/41	54	F	230/120	9.51	1.85	2.00	1.89	1.80	1.89	
71	3/28/41	40	M	230/130	12.38	4.48	6.52	2.67	5.89	4.89	
72	3/27/41	28	F	260/160	8.08	4.60	2.97	3.22	3.75	3.64	
88	3/31/41	38	F	240/120	8.69	4.12	3.25	3.49	2.77	3.41	
97	3/24/41	56	F	256/110	9.85	2.58	2.57	2.27	2.05	2.37	
Mean						3.55	3.92	3.47	3.58	3.63	
Maximum										8.80	
Minimum										1.75	
Toe Tips											
28					8.41	3.82	3.47	3.54		3.61	87
37					8.69	6.12	5.93	5.43	4.80	5.57	74
40					7.36	1.60	1.47	1.52	1.96	1.92	99
44					11.36	0.92	0.83	0.79	0.62	0.75	32
58					7.62	3.29	2.86	3.27	3.21	3.15	75
70					7.61	1.43	1.17	1.31	1.05	1.25	66
71					8.49	3.24	3.65	3.69	2.85	3.36	69
72					8.02	2.31	1.31	1.38	1.35	1.58	43
88					8.02	1.75	1.60	1.38	1.50	1.56	51
97					8.60	0.92	0.85	0.70	0.70	0.79	33
Mean						2.54	2.31	2.30	2.00	2.29	63
Maximum										6.12	
Minimum										0.62	

TABLE III

RATE OF SWEATING (MG./SQ. CM. SKIN AREA/15 MIN.) MEASURED SIMULTANEOUSLY ON THE RIGHT INDEX FINGER TIP AND RIGHT SECOND TOE TIP OF 8 SENILE, WHITE, RESTING ADULTS

SUBJECT NO.	DATE	AGE (YEARS)	SEX	BLOOD PRESSURE (MM. HG)	AREA OF SKIN (SQ. CM.)	FIRST 15 MIN.	SECOND 15 MIN.	THIRD 15 MIN.	FOURTH 15 MIN	MEAN 15 MIN.	RATE OF SWEATING AS % OF FINGER RATE
					Finger Tips						
22	4/ 2/41	78	M	168/88	11.41	2.12	2.68	2.52	2.48	2.45	
27	4/ 3/41	78	M	132/84	10.38	1.85	1.78	1.90	1.97	1.88	
41	4/ 1/41	71	M	110/60	11.14	2.01	2.12	2.03	2.18	2.09	
47	4/ 1/41	79	M	130/72	10.70	2.73	2.34	2.34	2.25	2.41	
63	4/ 3/41	85	M	148/80	11.28	2.45	1.81	2.35	2.00	2.15	
69	3/25/41	75	M	148/70	10.79	2.44	2.39	1.71	2.87	2.35	
93	4/ 2/41	81	M	140/64	9.83	2.33	2.22	2.13	2.07	2.19	
95	3/25/41	70	M	136/80	10.39	2.08	2.61	2.34	2.33	2.34	
Mean						2.25	2.24	2.17	2.27	2.23	
Maximum										2.87	
Minimum										1.71	
					Toe Tips						
22					7.32	0.96	0.87	1.30	0.70	0.96	39
27					9.22	1.37	1.17	1.11	1.25	1.22	65
41					7.92	1.26	1.14	1.14	1.01	1.14	55
47					9.15	1.24	1.17	1.03	0.98	1.11	47
63					9.56	0.83	0.78	0.68	0.72	0.75	35
69					8.30	1.55	1.19	1.43		1.39	59
93					8.61	1.35	1.18	0.85	1.08	1.12	51
95					8.71	1.23	1.19	0.88	1.03	1.09	47
Mean						1.22	1.09	1.05	0.97	1.08	48
Maximum										1.55	
Minimum										0.68	

The mean rate from the toe tips was 1.95 mg.,* and the minimum and maximum variations were 0.67 and 6.81, respectively (Table I).

In the patients with arterial hypertension the loss from the finger tips was 3.63 mg., with minimum and maximum variations of 1.75 and 8.80, respectively, and, from the toe tips, 2.29 mg., with minimum and maximum variations of 0.62 and 6.12, respectively (Table II).

In the senile subjects the loss from the finger tips was 2.27 mg., with minimum and maximum variations of 1.71 and 2.87, respectively, and, from the toe tips, 1.08 mg., with minimum and maximum variations of 0.68 and 1.55, respectively (Table III, Fig. 1).

The loss in patients with hypertension was essentially the same, therefore, as in normal subjects. The senile subjects, on the other hand, lost much less. In all groups the loss from the toe tips was practically one-half that from the finger tips; the variations were from 32 to 99 per cent but were much less in the senile groups.

TABLE IV

RATE OF SWEATING (MG./SQ. CM. SKIN AREA/15 MIN.) OF FINGER TIPS (F) AND TOE TIPS (T) OF PAIRS OF NORMAL, RESTING SUBJECTS, STUDIED SIMULTANEOUSLY

SUBJECT NO.	DATE	PART	AREA OF SKIN (SQ. CM.)	FIRST 15 MIN.	SECOND 15 MIN.	THIRD 15 MIN.	FOURTH 15 MIN.	MEAN 15 MIN.
6 and 96	5 /6/41	F	8.64	1.31	1.23	1.71	1.28	1.38
		T	8.60	1.86	0.70	1.17	1.05	1.20
		F	6.90	2.97	2.59	3.12	8.74	4.37
		T	6.84	1.64	1.75	2.19	3.01	2.15
14 and 86	5/ 7/41	F	7.56	4.03	3.66	2.76	2.74	3.30
		T	7.98	1.56	1.04	1.13	1.17	1.23
		F	7.62	3.33	2.93	2.23	1.84	2.58
		T	7.96	1.62	1.34	0.72	0.67	1.09
86 and 49	5/13/41	F	7.62	3.18	5.59	2.81	5.46	4.26
		T	7.96	1.42	1.46	1.09	0.89	1.22
		F	8.66	5.57	4.50	3.46	2.75	4.07
		T	8.44	2.71	2.30	1.67	1.34	2.00
54 and 96	5/16/41	F	9.08	8.37	7.02	7.16	5.54	7.02
		T	8.29	2.24	1.62	1.91	1.91	1.92
		F	6.90	4.35	2.78	3.52	3.43	3.52
		T	6.84	1.55	1.37	1.21	0.91	1.26

There were marked variations in the rate of sweating from person to person, and from fifteen-minute period to fifteen-minute period in the same person. The variation from period to period was greatest in normal and hypertensive subjects and least in the senile ones. In fact, the senile subjects were noteworthy for their constancy. In one of the subjects (Subject 86, Table IV) the mean rate of sweating of the finger tip was only three-fifths as rapid on one day as it was six days later, whereas in the toe tip it was only slightly less. The variations were always much greater in the fingers than in the toes. Similar results were obtained on Subject 96 (Table IV).

*The calculation is always given in milligrams per square centimeter per fifteen minutes.

When normal subjects were studied simultaneously in pairs, the rate of water loss increased in the finger or toe, or both, of one, while it remained the same or actually decreased in the other (Table IV). The variations from part to part in each of the pairs of subjects were discordant. The rate of sweating of the right and left index fingers or the right and left second toes also varied discordantly (Table V).

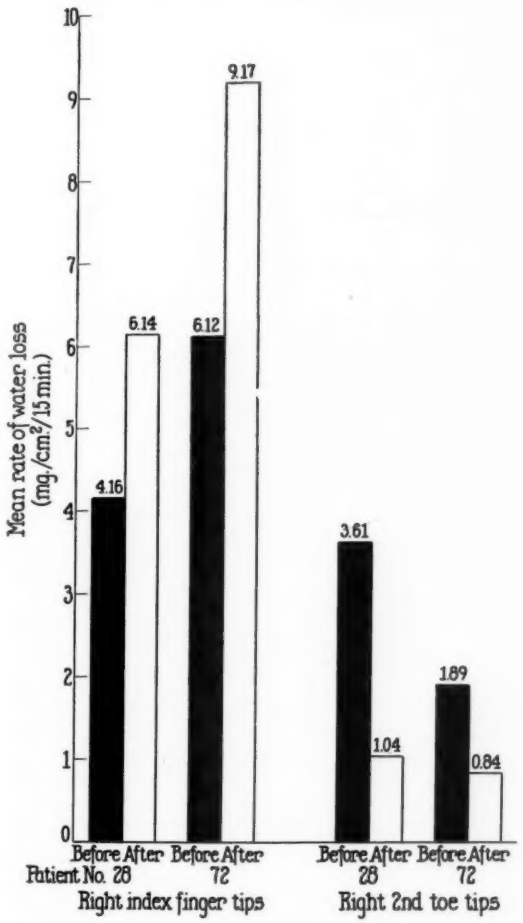

Fig. 2.—The rate of sweating of the tips of the fingers and toes of two hypertensive subjects before, and three weeks after, bilateral sympathectomy (ninth thoracic sympathetic nerve to first lumbar and the celiac and aortic renal plexuses).

In hypertensive patients whose lower thoracic and lumbar sympathetic nerves had been cut and the coeliac and aortic renal ganglia excised, a decrease of more than half the rate of water loss from the second toe and an increase of about half the rate from the index finger were found (Fig. 2). These differences were great enough for subjects and observers to detect by qualitative methods.

TABLE V

THE RATE OF SWEATING (MG./SQ. CM. SKIN AREA/15 MIN.) OF RIGHT AND LEFT INDEX FINGER TIPS OF RESTING SUBJECTS, STUDIED SIMULTANEOUSLY

SUBJECT NO.	PART	AREA OF SKIN (SQ. CM.)	FIRST 15 MIN.	SECOND 15 MIN.	THIRD 15 MIN.	FOURTH 15 MIN.	MEAN 15 MIN.	SWEATING RATE OF LEFT FINGER AS % OF RIGHT	DIAGNOSIS
2	Right	11.22	2.48	3.23	2.91	2.78	2.85	- 3	Normal
	Left	10.97	3.50	1.58	3.22	2.81	2.76		
3	Right	10.23	2.48	2.13	2.09	1.87	2.15	-15	Normal
	Left	10.63	2.25	1.67	1.60	1.80	1.83		
24	Right	7.56	2.39	4.72	5.22	6.42	4.69	- 5	Normal
	Left	7.17	1.92	3.85	5.43	6.71	4.48		
31	Right	8.85	4.31	5.88	5.10	6.96	5.56	+ 2	Normal
	Left	8.81	6.92	5.51	5.37	4.95	5.69		
54	Right	9.08	5.81	5.30	5.15	5.59	5.47	+ 1	Normal
	Left	8.57	5.95	5.80	4.83	5.41	5.50		
37	Right	10.73	4.40	8.70	8.01	8.80	7.48	- 2	Hypertension
	Left	10.73	6.13	6.80	8.00	8.51	7.36		
40	Right	9.31	1.84	1.99	1.98	1.92	1.93	+12	Hypertension
	Left	8.35	2.20	2.12	2.01	2.35	2.17		
58	Right	8.67	4.81	3.56	4.65	3.71	4.19	-12	Hypertension
	Left	7.95	3.77	4.35	3.60	2.97	3.67		
71	Right	12.38	4.08	2.96		2.60	3.36	+ 4	Hypertension
	Left	11.62	3.48	3.53		3.53	3.51		
72	Right	8.08	4.60	2.97	3.22	3.75	3.64	+20	Hypertension
	Left	7.46	5.25	3.47	3.67	5.16	4.38		
27	Right	10.38	1.85	1.78	1.90	1.97	1.88	+21	Senility
	Left	10.48	2.09	2.08	2.48	2.43	2.27		
41	Right	11.14	2.01	2.12	2.03	2.18	2.09	+ 8	Senility
	Left	10.77	2.46	1.95	2.37	2.25	2.26		
47	Right	10.70	2.73	2.34	2.34	2.25	2.41	+ 9	Senility
	Left	10.36	3.19	2.62	2.36	2.29	2.62		
93	Right	9.83	2.33	2.22	2.13	2.07	2.19	-15	Senility
	Left	9.20	1.46	1.86	2.47	1.70	1.87		
95	Right	10.39	2.08	2.61	2.34	2.33	2.34	+ 6	Senility
	Left	9.50	2.56	2.56	2.49	2.26	2.47		
Mean								±9	
Maximum								21	
Minimum								1	

There were great variations in the rate of sweating of the finger and toe tips of a normal subject when measurements were made continuously for 12.25 hours, with collections every fifteen minutes (Fig. 3). Shortly after each meal (noon and evening), the rate increased for about ninety minutes. When the subject fell asleep, it reached a minimum which was very constant.

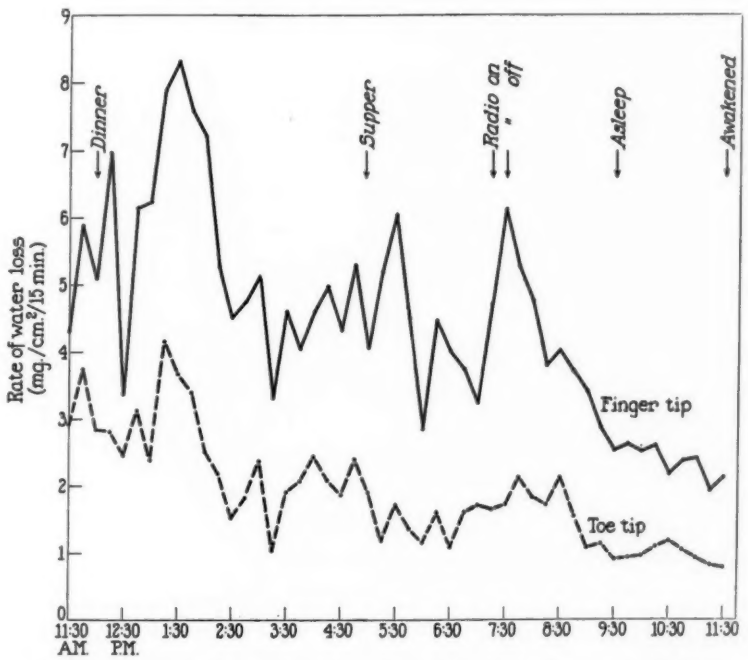

Fig. 3.—Changes in the rate of sweating measured for fifteen-minute periods during an observation of 12.25 hours.

The rate of water loss of a patient with advanced Raynaud's disease and scleroderma of the upper extremities whose cervical sympathetic nerves had been cut eight years before was 1.12 mg. in the right, and 1.25 mg. in the left, index finger tip per square centimeter per fifteen minutes. These rates were about one-third as rapid as in the same parts of normal subjects, and less than the normal minimum value. The rate of water loss from the right second toe tip was 1.85 mg. per square centimeter per fifteen minutes, a value similar to that of the normal group. Early Raynaud's disease of the toes was present in this patient.

DISCUSSION

The values for the rate of water loss from the tips of the fingers and toes of normal subjects are greater than in those previously reported.[3] In the first series of normal persons the loss from the fingers was 2.10 mg. per square centimeter per fifteen minutes, and, from the toes, 1.42

(calculated for the area of the skin, not the total surface area), whereas, in the present series of normal subjects, it was 3.59 from the fingers and 1.95 from the toes. Many of the subjects were studied in both series. The conditions were the same except for two factors: (1) The first study was conducted during the hot months of June, July, and August, 1940, and the present study, during the cool period of the last week of March, April, and the first two weeks of May, 1941. Although the temperature and humidity of the room were the same, subjects who entered the room during the hot summer months invariably commented on the coolness of the room, whereas those who entered this spring failed to make such comments. In fact, most of the subjects considered the room warm. That this is an important cause for the differences is not supported by the studies of Winslow, Herrington, and Gagge,[5] who stated: "During the summer season, the mechanism of sweat secretion is in better working order than in winter so that the body responds to a given condition (in the zone of evaporation regulation) with a somewhat higher secretory activity." More extensive studies, over a period of a year, would, nevertheless, be necessary before a definite conclusion regarding seasonal influences could be reached. (2) In the first series, psychic disturbances played a role because of the presence of laboratory equipment in the same room with the subjects; this was markedly reduced in the second series.[4] The importance of this factor could not be estimated, but it is true that many of the subjects were well acquainted with the laboratory and were not likely to be upset by it. There are many variables, however, in a person's daily and yearly activities that may be the basis of physiologic differences. The studies on patients were interspersed with those on the normal persons of the present series, and all observations were completed before the summer season began.

The marked variations in the same person from time to time and from one anatomic region to another at the same time were expected. The number of sweat glands which function at a given time is, as is well known, quite variable.[5, 6] Sweating is influenced by many factors, including the psyche and fatigue, both of which lack uniformity, and both of which are always exerting some influence in any physiologic study on conscious persons.

In two subjects who were studied in the same room, in separate beds, under identical environmental conditions, there were discordant variations in their comparable anatomic parts (Table V). Such variations must be the result of conditions unrelated to the room. Furthermore, although the mean rate of sweating in the toes was always essentially one-half the mean rate in the fingers, this was not true for each individual measurement. The ratio of the rates of sweating in fingers and toes in any one subject varied markedly.

Under the conditions of our observations, the palmar surfaces of the hands were noticeably moist when the rate of water loss from the finger tip was 5 mg. or more.

The mean rate of sweating in the patients with hypertension was about the same as that in the normal subjects. This fact is interpreted to mean that, under conditions of rest and quiet, the sympathetic tone, as indicated by its effect on sweating, is about the same in hypertensive as in normal persons. This is in keeping with the observations of others who studied the cardiovascular system and found no evidence of increased sympathetic tone.[1, 2] Under conditions of stress and strain an increase may nevertheless exist.

The rate of sweating in the senile subjects was definitely less rapid and much less variable than in the normal persons. This is probably one of the general manifestations of reduced physiologic activity which are known to occur in senile persons. No attempt was made to learn what part this was of their total capacity to sweat. It is unknown whether the low rate of sweating is due to a decrease in the number of sweat glands, to partial atrophy, to decreased function, or to all three factors.

SUMMARY

The rate of water loss from the tip of the index finger and second toe of normal subjects was very variable. There were variations from one period of fifteen minutes to another, from finger to toe, from right finger to left finger, and from day to day in the same subject. The mean rate of sweating in the toe tips was approximately one-half that in the finger tips, although this ratio could be variable. The rate of sweating varied markedly from person to person under identical conditions of observation.

In the patients with arterial hypertension the rate and variations of water loss from the finger and toe tips were about the same as in the normal subjects. This suggests that, in resting persons with hypertension, sympathetic activity is no greater than in normal subjects.

In senile subjects the rate of water loss was much less than in the normal subjects and patients with hypertension. Furthermore, the rates from period to period were much less variable. In fact, the senile subjects were outstanding for the constancy with which they lost water. This may be part of the reduced physiologic activity which is known to occur in senile persons.

REFERENCES

1. Prinzmetal, M., and Wilson, C.: The Nature of the Peripheral Resistance in Arterial Hypertension With Special Reference to the Vasomotor System, J. Clin. Investigation **15**: 63, 1936.
2. Pickering, G. W.: The Peripheral Resistance in Persistent Arterial Hypertension, Clin. Sc. **2**: 209, 1936.

3. Neumann, C., Cohn, A. E., and Burch, G. E.: A Quantitative Method for the Measurement of the Rate of Water Loss From Small Areas, With Results for Finger Tip, Toe Tip, and Postero-Superior Portion of the Pinna of Normal Resting Adults, Am. J. Physiol. **132:** 748, 1941.
4. Neumann, C., Cohn, A. E., and Burch, G. E.: A Study of the Influence of the Furniture of an Examining Room on the Peripheral Blood Vessels of Normal, Hypertensive, and Senile Subjects (to be published).
5. Winslow, C. E. A., Herrington, L. P., and Gagge, A. P.: The Reactions of the Clothed Human Body to Variations in Atmospheric Humidity, Am. J. Physiol. **124:** 693, 1938.
6. Kuno, Y.: Variations in Secretory Activity of Human Sweat Gland, Lancet **1:** 299, 1938.

INFECTED THROMBI OF THE HEART

JAMES R. LISA, M.D., AND CYRIL SOLOMON, M.D.
NEW YORK, N. Y.

DURING the past two and one-half years we have encountered at the New York City Hospital, Welfare Island, several cases of septic thrombosis of the heart. The thrombi differed from the usual septic mural thrombi in that they were not associated with acute bacterial endocarditis, valvular or mural. In the majority of cases, they occurred in patients who came under observation because of cardiac failure. In several instances it was possible to ascertain the original site from which the pyogenic organisms reached the heart. Since we were unable to find in medical literature any mention of similar cases, and because this lesion offers an explanation of cardiac failure in some patients, this series is being reported. During the same period, several other thrombi were investigated from the bacteriologic standpoint with negative results.

CASE REPORTS

CASE 1.—The patient, a young Negro, aged 31 years, was admitted to the medical service of Dr. B. F. Donaldson Feb. 4, 1939, with severe congestive failure. For three years he had been under observation at various institutions because of congestive failure due to rheumatic heart disease. The final phase began one week before he entered the New York City Hospital. The course was rapidly progressive; the temperature ranged from 97.6° to 101° F.; tachycardia and a pulse-temperature discrepancy were constant; and jaundice developed. The electrocardiogram showed normal sinus rhythm, a rate of 100, a P-R interval of 0.24 sec., no axis deviation; T_1 and T_2 were diphasic, and QRS was slurred. On the third hospital day sudden cardiac collapse appeared, and death followed in one hour.

Autopsy (5436).—The heart weighed 525 Gm. In the right auricular appendage there were numerous soft, round, yellow thrombi, with dirty yellow fluid contents, from which a hemolytic *Staphylococcus aureus* was cultured. The auricular muscle showed extensive, acute necrosis, but bacteria were not demonstrable in sections. Mitral stenosis was present (healed), and the aortic valve was the seat of a chronically active lesion. The left ventricle showed several Aschoff bodies. The upper lobe of the right lung was the seat of an acute, embolic, suppurative pneumonia; cultures were not taken.

CASE 2.—The patient, a white man, aged 74 years, was admitted to the medical service of Dr. B. F. Donaldson March 22, 1939. He had had mild dyspnea on exertion and edema of the ankles for one year. For three weeks the symptoms had been much more severe. He was acutely ill and jaundiced and was edematous up to the abdominal wall. The heart was enlarged; the sounds were of fair quality;

From the Pathological Laboratory, City Hospital, Welfare Island, Department of Hospitals, New York.
Received for publication July 10, 1941.

the rate was rapid; and the beating was irregular. The blood pressure was 140/80. The course was progressive, with rising temperature, tachycardia, increasing weakness of the pulse, pulmonary signs not very suggestive of pneumonia, and death on the third day. A pulse-temperature discrepancy was present from the beginning and increased steadily; during the last thirty-six hours the pulse was too rapid and weak to count accurately.

Autopsy (5488).—The heart weighed 675 Gm. In the right auricular appendage were a few globular, soft thrombi which contained creamy yellow pus; the culture yielded pneumococcus Type III. In the underlying myocardium there were numerous foci of degeneration, with polymorphonuclear infiltration and Gram-positive cocci. The ventricular muscle showed extreme cloudy swelling, without cellular reaction. The coronary arteries were moderately sclerotic. The right lung was the seat of an acute lobar pneumonia (upper and lower lobes). The lung was not cultured, but the bacteria which were seen in the sections looked like pneumococci.

CASE 3.—The patient, a white man, aged 48 years, was under observation on two occasions. He was first admitted to the medical service of Dr. J. H. Cudmore on Feb. 10, 1939, because of dyspnea on exertion, weakness, and headaches. The onset was five weeks previously. High blood pressure had been discovered one year before. There were moderate cyanosis, an enlarged heart with good sounds, a blood pressure of 195/130, a low fever (100.4° F.), a pulse rate of 112, and albuminuria (1 plus). The renal function tests showed moderate inability to concentrate. The nonprotein nitrogen content of the blood was 33 mg. per cent. The electrocardiogram showed normal sinus rhythm, a rate of 100, and right axis deviation; T_1 was of low amplitude, and QRS was slurred. He had one severe attack of nocturnal dyspnea, with intense cyanosis. Signs of bleeding duodenal ulcer appeared, necessitating transfusion. After seven weeks he improved and was discharged (March 29, 1939).

He was readmitted May, 19, 1939, to the medical service of Dr. John Carroll. The cardiac symptoms had recurred after two weeks and were accompanied by failing vision. The most prominent features throughout the final period of observation of ten weeks were paroxysmal dyspnea, cyanosis, and increasing anemia. On one occasion there was a tarry stool. The blood pressure remained elevated. The urine had a fixed specific gravity of 1.010, and contained casts, erythrocytes, and leucocytes. The nonprotein nitrogen rose from 35 to 150 mg. per cent. The Van Slyke index dropped to 17 per cent. The electrocardiogram showed normal sinus rhythm, a rate of 107, a P-R interval of 0.16 sec., and no axis deviation. T_1 was broad; T_2 and T_3 were depressed; and QRS was slurred. The temperature varied from 99° to 100° F.; during the last few days it gradually rose to 102° F. The pulse was consistently rapid, and there was a constant pulse-temperature discrepancy. Death occurred in coma on July 28, 1939.

Autopsy (5579).—The heart weighed 600 Gm. The right auricular appendage contained two large, soft, purulent thrombi, from which Type III pneumococcus was isolated. The underlying muscle was acutely necrotic. In the left ventricle there were several acute miliary infarcts and small abscesses. There was a bilateral acute, lobar pneumonia, and the sections showed bacteria which resembled pneumococci.

CASE 4.—The patient, a 44-year-old Negro, was admitted to the medical service of Dr. Charles Dillon on June 9, 1939, where she remained until her death on September 2. Her illness dated back two years and was characterized by a steadily progressive cough, with sputum which was neither bloodtinged nor foul, weight loss, and dyspnea on exertion. The physical signs were largely cardiac. The heart

was enlarged; the neck veins were engorged; the liver was tender and enlarged; and the blood pressure was 220/150. During July there was a period of profuse perspiration, dyspnea, equivocal signs at the base of the right lung, bloodtinged sputum, low-grade fever, and rise of the nonprotein nitrogen to 60 mg. per cent. One attack of severe angina occurred. With diminution of the amount of sputum, the lung signs became more definite. The last six weeks were characterized by neurological manifestations, namely, permanent urinary and fecal incontinence, variable lethargy, Cheyne-Stokes respiration, and periods of quiet delirium. The nonprotein nitrogen level fell to 32 mg. per cent. The blood pressure remained high. Death occurred in coma. During the last few hours the pulse became almost imperceptible.

Autopsy (5602).—The heart weighed 400 Gm. There was an acute diffuse pericarditis. A gray, purulent, mural thrombus was present in the right auricle, cultures from which revealed staphylococci and streptococci. The auricular muscle was acutely damaged, and in the left ventricle there were a few miliary infarcts. The lower lobe of the right lung contained a chronic, putrid abscess, and many of the veins at the periphery of this abscess were thrombosed. The organisms isolated were the same as those found in the heart. The brain showed multiple, cerebral cortical hemorrhages.

Fig. 1.—Case 5. Acute thrombosis of the anterior descending coronary artery (arrow) and massive myocardial infarction. In the left ventricle there are numerous, small thrombi of the recesses, and, in the right ventricle (arrow on the left), several larger, smooth thrombi. *Streptococcus hemolyticus* was isolated from a traumatic leg ulcer and the cardiac thrombi. The mitral and aortic valves are the seat of chronic rheumatic disease.

CASE 5.—The patient, a white man, aged 44 years, was admitted to the medical service of Dr. Charles Dillon on Sept. 4, 1939, because of an anginal attack which had occurred eight days before. The first attack, one year previously, had incapacitated him for only four days. Physical examination showed an acutely ill,

dyspneic, and cyanotic man. The heart was greatly enlarged, and the first sound at the apex was split. The blood pressure was 85/65. There were râles at the bases of both lungs. The temperature was 100° F.; the pulse rate, 120; and the respiratory rate, 32. The electrocardiogram showed normal sinus rhythm, a rate of 107, normal A-V conduction time, and left axis deviation; S-T_1 was slightly high, and QRS was broad, notched, and slurred. There was a small ulcer on the right tibial surface which was the result of an injury received some time before. The temperature fluctuated to 102° F., and the pulse rate remained rapid (100 to 120). Death occurred suddenly on the fourth hospital day.

Autopsy (5605).—The heart weighed 500 Gm. It showed a chronically active rheumatic mitral and aortic valvulitis, severe arteriosclerosis of the coronary arteries, acute thrombosis of the anterior descending artery, acute massive cardiac infarction, and many smooth mural thrombi of both ventricles and the left auricle (Fig. 1). Histologically, all parts of the wall contained numerous miliary infarcts. In the lungs there were numerous recent arterial emboli and acute infarctions. Cultures of the leg ulcer and cardiac thrombi revealed *Streptococcus hemolyticus*. No bacteria were demonstrated in sections of the heart muscle or in the thrombus of the coronary artery.

CASE 6.—The patient, a white man, aged 68 years, was admitted to the medical service of Dr. W. L. Reardon Oct. 6, 1939. He had always been well until eight days previously, when he had a typical anginal attack. The heart did not appear to be enlarged; the first mitral sound was split; the blood pressure was low (80/60); the neck veins pulsated; and the liver was enlarged and tender. The electrocardiogram showed normal sinus rhythm, a rate of 93, normal A-V conduction time, and a tendency to right axis deviation. S-T_1 had a high take-off; T_2 was broad; T_3 was inverted; S-T_4 had a low take-off; and QRS was of low voltage in all leads. A pericardial friction rub appeared. Signs of pulmonary consolidation, persistent tachycardia, and a fluctuating temperature followed. Death occurred on the fifth day.

Autopsy (5654).—The heart weighed 500 Gm. The surface was covered by a thick fibrinous exudate. In the left auricle there was a large globular thrombus which projected into the cavity from the appendage. The coronary arteries were markedly sclerotic; the left descending branch was occluded by a recent thrombus, and there was an acute, massive infarction. *Streptococcus hemolyticus* was isolated from the pericardium, and *Streptococcus viridans* from the auricular thrombus. Histologic examination showed numerous miliary infarcts in the walls of both auricles. The lungs were the seat of acute confluent bronchopneumonia.

CASE 7.—The patient, a white woman, aged 24 years, was admitted to the medical service of Dr. W. L. Whittemore Oct. 18, 1939. She had been under observation at another institution because of a birth injury. On Sept. 6, 1939, an exploratory laparotomy was performed at another hospital, and tuberculous peritonitis was found. After her discharge she developed a cough and then entered New York City Hospital. She appeared acutely ill. Her lungs were filled with râles. The surgical incision was healed, but the abdomen was tense and slightly tender. The heart rate was 118, and the blood pressure, 85/60. Toward the end of the month there were frequent attacks of paroxysmal dyspnea. On the twelfth hospital day, evisceration through the incision occurred. The temperature ranged from 98° F. to 102° F. The pulse remained rapid and there was an increasing pulse-temperature discrepancy. Death occurred on Nov. 11, 1939.

Autopsy (5665).—The heart weighed 350 Gm. The myocardium was flabby and muddy in color. There were numerous purulent mural thrombi in both auricles, and the left ventricle contained a large thrombus which extended from apex to base

(Fig. 2). *B. coli* was cultured from these thrombi. Histologic examination showed acute interstitial myocarditis which was most marked in the deeper layers of muscle. The base of the right auricular thrombus was beginning to organize. In addition, there were tuberculosis of the peritoneum, mesenteric lymphatics, cecum, and lungs, and acute peritonitis due to fecal contamination.

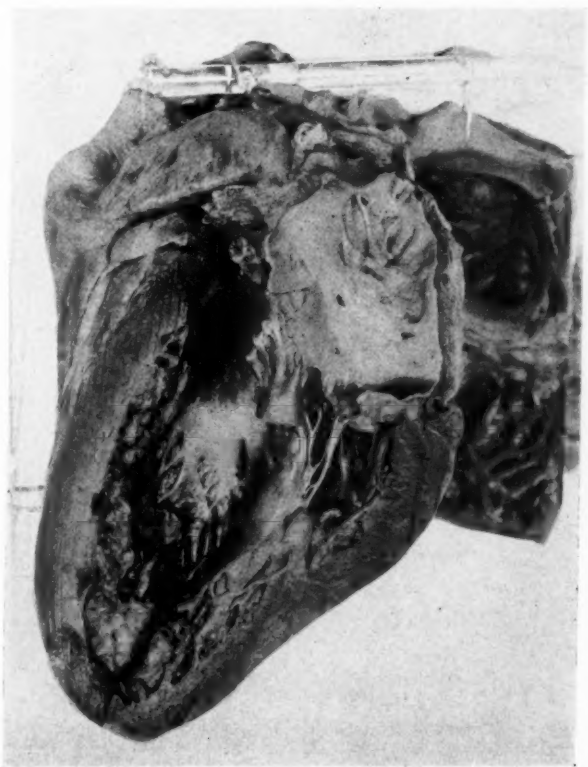

Fig. 2.—Case 7. Acute infected thrombi of the left ventricle and right auricle. In the left ventricle they extend from apex to base; in the right auricle they are multiple. Similar thrombi were present in the left auricle. *B. coli* was isolated. The cardiac infection was secondary to acute peritonitis, superimposed, by fecal contamination, on a tuberculous peritonitis.

CASE 8.—The patient, a white woman, aged 74 years, was admitted Dec. 21, 1939, to the neurologic service of Dr. John Nolan because of a left-sided hemiplegia of thirty-six hours' duration. She improved steadily until Feb. 9, 1940, when she developed a Type XXI pneumococcal pneumonia. Sulfapyridine was given, and the temperature returned to normal in three days. Four days later the temperature again rose, reaching 105.6° F.; chemotherapy was ineffectual, and death occurred about thirty-six hours later. The pulse rate and temperature remained in normal proportion.

Autopsy (5776).—The heart weighed 275 Gm. The myocardium was flabby and of poor color. Near the apex of the left ventricle there were three rounded, friable, yellow, mural thrombi, with necrotic centers. Nearby was a firmer pink-white thrombus (Fig. 3). Cultures revealed a non-chain-forming, Gram-positive coccus which failed to grow on subculture and could not be identified. Histologically, the ventricular muscle showed a few areas of miliary necrosis. The left lung was the seat of a patchy, acute bronchopneumonia which yielded Type XXI pneumococcus.

CASE 9.—The patient, a 68-year-old white man, was admitted with severe congestive failure to the medical service of Dr. W. L. Whittemore on Dec. 7, 1940. For seven years he had suffered from gradually increasing dyspnea which had resulted in little inconvenience. In February, 1940, he had a frank anginal attack. One week before entering the hospital he had a second very severe attack and became bedridden. He was very dyspneic and cyanotic. The neck veins pulsated, and the apex beat could not be palpated. The ventricular rate was 140 and regular, and the pulse rate was 120. There was dullness at the base of the left lung. The edge of the liver was hard and was palpable at the level of the umbilicus. The blood pressure was 90/80. Albuminuria was present, and the nonprotein nitrogen was 106 mg. per cent. The electrocardiogram showed normal sinus rhythm, a rate of 75, normal A-V conduction time (0.16 sec.), and no axis deviation. T_1 was inverted; T_2 and T_3 were of low amplitude; and there was slurring of QRS. Bilateral hydrothorax and ascites appeared, and death occurred from pulmonary edema after five days. The temperature rose only to 100.2° F. terminally. The pulse remained rapid (80 to 132) and was variable in force.

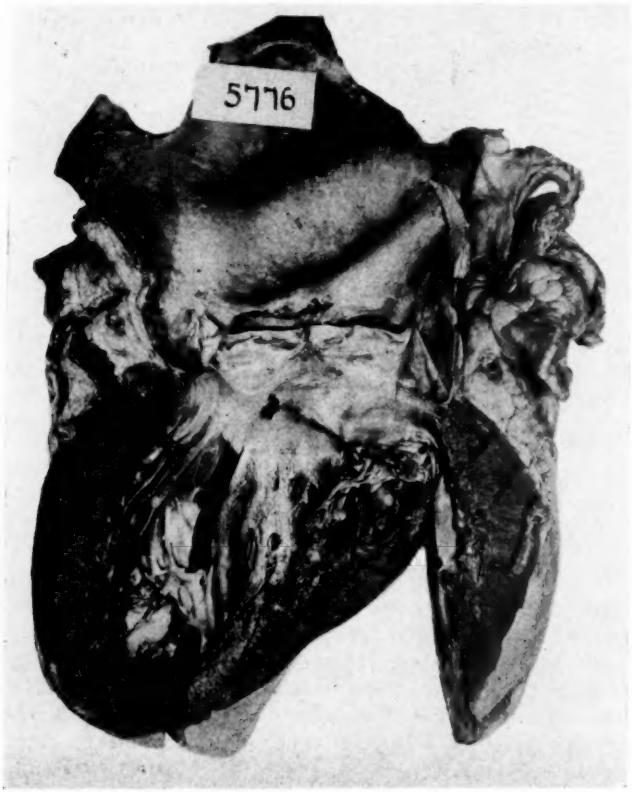

Fig. 3.—Case 8. Infected thrombi of the apex of the left ventricle, associated with Type XXI pneumonia. Non-chain-forming coccus was isolated from the thrombus, and pneumococcus Type XXI, from the lung.

Autopsy (6021).—The heart weighed 650 Gm. Both auricles contained sessile and pedunculated thrombi in the appendages and main chambers; the largest was 2 cm. in diameter. Their contents were dark red and slightly viscid and yielded

streptococci on culture. The underlying muscle was extensively necrotic and diffusely infiltrated with polynuclear cells. The left ventricle had a mottled appearance due to acute miliary infarctions. The coronary arteries were markedly sclerotic. An old, recanalized thrombus was present in the anterior descending branch. There was a bilateral, acute bronchopneumonia, from which streptococci were isolated.

Fig. 4.—Case 11. Multiple thrombi of right auricle. *Streptococcus hemolyticus* and *B. coli* were isolated from the peritoneal exudate, septic pulmonary emboli, and cardiac thrombi.

CASE 10.—The patient, a white woman, aged 69 years, was admitted in coma on Feb. 7, 1941, to the medical service of Dr. B. F. Donaldson. One week before admission coma occurred suddenly, followed by a short period of recovery and a recurrence. Physical examination was essentially negative except for an enlarged heart and a blood pressure of 140/110. The course was that of fluctuating coma. Death occurred on the fifth day. The temperature rose from 99° F. to 104° F. The pulse rate remained in normal relation to the temperature.

Autopsy (6071).—The heart weighed 350 Gm. There were numerous soft, round, mural thrombi in the left ventricle, from apex to base, arising between the columnae carneae. The contents were fluid and yielded a non-chain-forming coccus on culture. The coronary arteries were markedly sclerotic, and the left circumflex branch was occluded by an old, recanalized thrombus. Histologically, the unscarred portion of the ventricle showed numerous acute, miliary infarctions. There were a bronchogenic carcinoma, acute lobular pneumonia, marked cerebral arteriosclerosis, and a small cerebral infarction.

CASE 11.—The patient, a 66-year-old Negro, was admitted April 25, 1941, to the surgical service of Dr. F. Bancroft because of chronic ulcers of the legs. The only additional features were a severe anemia, an enlarged heart, and a blood pressure of 168/80. On May 6, she complained of abdominal pain, vomited, and had an

ill-defined, slightly tender mass in the right lower quadrant. The anemia became more severe. Signs of obstruction appeared; the temperature fluctuated to 102.4° F.; and the pulse became rapid. Death occurred in one week. During the last forty-eight hours the pulse rate became so rapid that it could not be counted accurately.

Autopsy (6167).—The heart weighed 485 Gm., and was covered by a fibrinous exudate. In the right auricle there were numerous soft, friable, mural thrombi (Fig. 4). The myocardium was a pale yellowish-brown. The coronary arteries were slightly sclerotic. There were several miliary infarcts in the left ventricle. The lungs showed multiple, acute, arterial emboli and acute infarctions. Acute, general peritonitis, secondary to acute appendicitis, with rupture, and a periappendiceal abscess were found. Cultures from the peritoneum, pulmonary emboli, and cardiac thrombi revealed hemolytic streptococci and colon bacilli, the former predominating.

DISCUSSION

Parietal thrombi of the heart are well known. According to Kaufmann,[1] they are usually regarded as secondary to dilatation and congestion caused by cardiac lesions, or to acute and chronic changes in the myocardium which result in slowing of, and eddy formation in, the blood current in the deep recesses, or to local degenerative changes of the endocardium. Harvey and Levine[2] also stated that the two most frequent causes are myocardial degeneration secondary to coronary artery disease, and improper functioning of the auricles. Although they have sometimes been described as puriform, it is generally believed that the softening is due to autolysis. An infectious type of decomposition has not been considered seriously. In the present series, pathogenic bacteria were isolated from the thrombi in each instance.

The appearance of the thrombi was striking. They were usually globular, perfectly smooth, yellow or gray in color, and soft in consistency. The contents were either frankly purulent, muddy, viscid, or sanguineous.

The sites were similar to those at which noninfected thrombi are usually found. The right auricle alone contained thrombi in five cases; the left auricle, in one, and the left ventricle, in two. More than one chamber was affected in the other five cases. Both auricles were involved once, and three chambers twice. In eight of the eleven cases the right auricle was involved, which is a higher percentage than was found by Harvey and Levine in their study of noninfected thrombi.

Bacteriologic investigations were complete in three cases. A mixture of staphylococci and streptococci was obtained in Case 4 from the lung abscess and thrombi. Streptococci were isolated from the lung and heart in Case 9. In Case 11, cultures revealed *Streptococcus hemolyticus* and *B. coli* in the peritoneal exudate, pulmonary emboli, and heart.

The bacteriologic evidence was less complete in the other cases, but necropsy supplied data which were suggestive of the original focus of infection. Case 5 was almost the same as Case 11, i.e., there were an

infection below the diaphragm, pulmonary embolism, and involvement of the heart. Hemolytic streptococci were isolated from the leg ulcer and heart; the pulmonary emboli were not cultured. In Case 1, a hemolytic *Staphylococcus aureus* was found in the heart; the lung was the seat of an embolic, suppurative pneumonia, but no culture was obtained. In Cases 2 and 3 the presence of a croupous pneumonia offered an adequate explanation for the presence of a pneumococcus in the heart. Case 8 appeared to be similar. A Type XXI pneumococcus was identified in the sputum before death and isolated from the lung at necropsy. The organism from the heart failed to grow, possibly because of the intensive chemotherapy which had been employed. Although this organism was not definitely identified, the evidence strongly suggested that it probably was a pneumococcus. In Cases 6 and 10 there was also a pneumonia, but in neither were the lungs cultured. In Case 7 there was a *B. coli* infection arising from the peritoneum, but without embolic pulmonary manifestations. We have observed in other infections caused by enteric organisms that the lungs may be unaffected, so that such a course, although not common, is not unknown. In ten of the eleven cases, therefore, the infection in the heart appeared to be secondary to the pulmonic lesion.

It is of interest to speculate upon the routes by which the heart could have become infected. The high incidence of pneumonia suggests that the original site of infection was most probably the lung, either as a primary process or as a secondary embolic pneumonia. In a recent communication, Hamman[3] stressed the role of embolism in acute occlusion of the large branches of the coronary arteries and mentioned thrombi of the pulmonary veins in suppurative processes. He reported one case in which there was a chronic, interlobar abscess. In the present series there were two instances of acute coronary occlusion. Suppurative pneumonia was present in Case 5, and non-necrotic pneumonia in Case 6. In neither were pulmonary thrombi observed. However, thrombi do not seem to be essential. One of us (J. R. L.)[4] previously reported that an infected embolus caused coronary occlusion in a case of pneumococcal pneumonia in the absence of pulmonary thrombi. The determining factor in its localization seemed to be the pre-existing, severe coronary disease. This factor was also present in both instances in this series.

An embolic mechanism may have played a part in five other cases. In Case 3 the left ventricle showed numerous miliary abscesses. In Case 4 there were pulmonary thrombi at the periphery of a chronic lung abscess. Acute miliary infarctions, with severe coronary disease, were widespread in Cases 9, 10, and 11. In Case 8, the localization of the thrombus suggested that it was arterial. In Case 7 the extensive involvement of the chambers suggested an arterial embolic spread which

was localized in the deep muscle because of the intact coronary circulation. Direct implantation from the cavities must likewise be considered seriously.

The possibility of a lymphatic spread must also be borne in mind. The rich anastomoses between the pulmonary lymphatics and the lymphatics at the base of the heart are well known and may constitute a route by which the heart can become involved secondary to pulmonary disease. We have often observed, at autopsies in this laboratory, an early pericarditis localized over the right auricle in cases of acute pneumonia. The thin auricular wall could easily become diffusely invaded, leading to the formation of an infectious thrombus. In the present series, the right auricle was affected more frequently than any other chamber.

The syndromes were entirely cardiac in five cases. In Cases 5, 6, and 9 there was angina; the pulmonary lesions were interpreted as secondary to the heart failure. No importance was attached to the leg ulcer in Case 5. Mild congestive failure had been present in Case 2 for a year, but the course was rapid during the last three weeks of life. When pneumonia attacks a patient with coronary sclerosis, it may precipitate acute cardiac failure, but it frequently is interpreted as a manifestation, not as the cause, of the failure. The same interpretation probably applies to Case 1. Such a course frequently is seen in cases of rheumatic heart disease, but the extent of the rheumatic myocarditis alone did not explain adequately the manifestations in this case.

In Case 3 the syndrome was both renal and cardiac. Death was caused by uremia. The lobar pneumonia was probably a terminal affair and enhanced the cardiac symptoms by the production of infarcts and abscesses.

The patients with abdominal disease presented symptoms which were masked partially by the surgical conditions. In Case 7, paroxysmal dyspnea and increasing tachycardia were prominent. Only an increasing weakness of the pulse and persistent tachycardia were noted in Case 11.

The patient with a pulmonary abscess (Case 4) first came under observation for severe cardiac failure, from which she apparently recovered. The pathologic changes in the heart were confined largely to the auricles.

In two cases the symptoms were entirely neurological. In Case 8 there were limited cardiac changes. In Case 10 there were limited cerebral changes which were not sufficient to explain the course; the extensive myocardial damage offered a much more satisfactory cause.

A febrile reaction was present in every instance. In Case 4, the temperature was elevated only during the period of cardiac failure. In several cases the temperature reached only 100° or 101° F.

A persistent discrepancy between the rate of the pulse and the height of the temperature was present in eight cases. In one (Case 4) it was present only during the last few hours, and in two (Cases 8 and 10) it was absent.

SUMMARY AND CONCLUSIONS

Eleven cases of infected thrombi of the heart are reported. In the majority of cases the patients came under observation because of cardiac failure or developed failure as a terminal phenomenon. In all but one case the infection of the heart appeared to be secondary to pneumonia. An embolic process was suggested in many instances. Some may have been lymphogenous in origin. All of the patients had some degree of fever. A discrepancy between the pulse rate and the temperature level was present in all instances in which there were manifest cardiac symptoms.

Bacteriologic investigation of cardiac thrombi offers a field which may lead to clarification of some cases of cardiac failure.

The bacteriologic work was carried out by Miss Sara A. Scudder, bacteriologist of the institution.

REFERENCES

1. Kaufmann, E.: Pathology (English Translation by Reimann, Philadelphia, P. Blakiston's Son & Co.), Vol. 1, pp. 79-80.
2. Harvey, E. A., and Levine, S. A.: A Study of Uninfected Mural Thrombi of the Heart, Am. J. M. Sc. **180**: 365, 1930.
3. Hamman, L.: Coronary Embolism, AM. HEART J. **21**: 401, 1941.
4. Lisa, J. R.: Unusual Findings in a Case of Acute Coronary Thrombosis, Arch. Path. **23**: 449, 1937.

SYPHILITIC CARDIOVASCULAR DISEASE AND BACTERIAL ENDOCARDITIS

SIMON KOLETSKY, M.D.
CLEVELAND, OHIO

THIS study was undertaken in order to ascertain the frequency with which syphilitic heart disease and bacterial endocarditis are associated with each other and also the importance of syphilis as a predisposing factor in the development of superimposed bacterial endocarditis. A review of 4,000 consecutive autopsies at the Institute of Pathology of the University Hospitals of Cleveland revealed five cases in which there was a diagnosis of both cardiovascular syphilis and bacterial endocarditis. However, four of these hearts also revealed stigmata of rheumatic fever, and this altered the significance of the syphilis in relation to the bacterial lesion. The results are at variance with several recent reports dealing with coexistent syphilis and bacterial endocarditis.[1-3]

REPORT OF CASES

CASE 1.—A 55-year-old white man was admitted to the hospital Jan. 6, 1931, and died March 12, 1931. His complaints on admission were shortness of breath and weakness of one year's duration and swelling of the legs of one month's duration. There was a history of a chancre at the age of 20 but no history of rheumatic fever. Physical examination revealed an enlarged heart, systolic and diastolic murmurs over the aortic area, and generalized edema. The blood pressure was 145/55. There were no petechiae or emboli, and the spleen was not palpable. Laboratory examination revealed a moderate anemia, microscopic hematuria, a strongly positive blood Wassermann reaction, and a blood urea nitrogen of 91 mg. per 100 c.c. The patient had a persistent, low-grade fever. No blood cultures were made. The clinical diagnoses were syphilitic heart disease, with aortic insufficiency, chronic glomerulonephritis, and congestive heart failure.

The diagnoses at autopsy were endocarditis lenta involving the aortic and mitral valves; syphilitic aortitis and aortic valvulitis; rheumatic heart disease, with chronic aortic and mitral valvulitis; cardiac hypertrophy and dilatation (730 Gm.); recent infarcts of the spleen; subacute diffuse glomerulonephritis; and chronic passive hyperemia of the viscera. Culture of the heart's blood yielded no growth. Bacterial stain of a vegetation showed Gram-positive cocci.

There was a patchy syphilitic lesion of the root of the aorta, involving especially the regions above the commissures (Fig. 1). The aortic valve showed marked rheumatic disease, i.e., thickening and retraction of the cusps, eversion of the free margins, and fusion of the left-right and right-posterior commissures. Syphilis of

From the Institute of Pathology, Western Reserve University, and University Hospitals of Cleveland.
Received for publication Aug. 27, 1941.

Fig. 1.—Case 1. Combined syphilitic and rheumatic disease of the aortic valve, with endocarditis lenta, in a 55-year-old white man. There are elevation and widening of the proximal portions of the raphes at commissures *A* and *B*. A vegetation is attached to the free margin of the posterior cusp adjacent to commissure *B*. The anterior mitral leaflet shows ulceration (*a*) and numerous vegetations.

In photographs of the aortic valve, *A* represents the left-right commissure; *B*, the right-posterior commissure; *C*, the left-posterior commissure; *lc*, the ostium of the left coronary artery; and *rc*, the ostium of the right coronary artery.

Fig. 2.—The mitral valve in Case 1. The anterior leaflet shows vegetations on the free margin (*a*) and adjacent chordae tendineae. Although no gross rheumatic disease is evident, microscopic examination revealed diffuse chronic valvulitis.

the aortic valve could not be diagnosed grossly. However, the proximal portions of the commissural raphes were elevated and widened, suggesting a superimposed syphilitic involvement. The left-posterior commissure showed no change. There was a nodular calcific deposit in the distal portion of the raphe at the left-right commissure, in the left and right cusps adjacent to this raphe, and in the base of the right cusp. Small, friable, grayish-red vegetations were attached to the free margin of the posterior aortic cusp near the right-posterior commissure and to the distal ventricular aspect of the raphe at the left-right commissure. Numerous vegetations were also present on the aortic surface of the anterior mitral leaflet, which showed extensive ulceration, and on the free margin and adjacent chordae tendineae of this leaflet (Fig. 2). There was no gross rheumatic disease of the mitral, tricuspid, or pulmonary valves.

Microscopic sections of the aortic valve through the commissural raphes revealed extension of the syphilitic lesion of the aorta into the ring of the valve, with irregular hyaline thickening and vascularity of the annulus fibrosus. The raphes were the seat of diffuse fibrosis, but vascularity and inflammation were confined largely to the ventricular aspect of the distal and basal portions just above the subaortic angle. Numerous sections of the aortic and mitral valves showed fibrosis, vascularity to the line of closure with capillaries, arterioles, and thick-walled small arteries, and lymphocytic infiltration. These changes involved both the ring and free portion and were most marked on the atrial side of the mitral valve and on the ventricular side of the aortic valve. The tricuspid and pulmonary valves and the left atrium showed no significant change. There were no Aschoff bodies in the myocardium. The vegetations were composed of masses of necrotic fibrinoid material and superficial colonies of bacteria. There were a slight exudation of lymphocytes and polymorphonuclears at the base and also an increase in the number of histiocytes and fibroblasts.

CASE 2.—A 47-year-old Negro was admitted to the hospital Feb. 11, 1933, and died Feb. 21, 1933. His complaints on admission were fever, chills, and pain in the left foot of two months' duration. He gave a history of injury to the left foot in August, 1932. He had a chancre at the age of 32; there was no history of rheumatic fever. On physical examination the heart was enlarged, and there were systolic and diastolic murmurs over the aortic area. The blood pressure was 130/50. The patient had a septic fever, anemia, microscopic hematuria, and conjunctival petechiae. There were no emboli, and the spleen was not palpable. Two blood cultures yielded *Streptococcus alpha*. The clinical diagnoses were streptococcus septicemia, acute bacterial endocarditis, with aortic insufficiency, tertiary syphilis, mild congestive heart failure, and bronchopneumonia.

The diagnoses at autopsy were organizing acute bacterial endocarditis involving the aortic, mitral, and tricuspid valves and the endocardium of the left ventricle; syphilitic aortitis; cardiac hypertrophy and dilatation (410 Gm.); recent infarcts of the right lung, kidneys, and spleen; and chronic passive hyperemia of the viscera. Culture of the heart's blood yielded *Streptococcus alpha*.

There was diffuse syphilis of the root of the aorta, with extension into the sinuses of Valsalva, but no involvement of the aortic valve. No conclusive gross evidence of rheumatic heart disease was present. The aortic, mitral, and tricuspid valves were the seat of bacterial endocarditis. The vegetations were large, grayish-red, and friable, and not firmly adherent to the endocardium. All three aortic cusps were involved extensively and largely destroyed (Fig. 3). Below the aortic valve, vegetations were attached to the membranous portion of the interventricular septum, which was superficially ulcerated, and to the base of the anterior mitral

leaflet. In the latter situation the lesions penetrated the leaflet and projected from its atrial aspect. A single, large, polypoid vegetation was attached to the line of closure of the tricuspid septal leaflet, and small vegetations were present on several adjacent chordae tendineae.

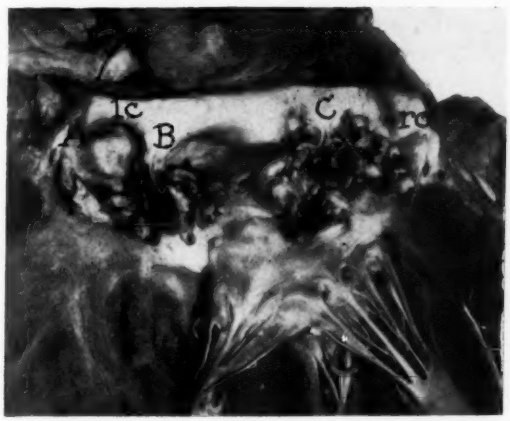

Fig. 3.—Case 2. Combined syphilitic aortitis and acute bacterial endocarditis of the aortic valve in a 47-year-old Negro. The base of the anterior mitral leaflet also shows vegetations.

Numerous microscopic sections of the central and lateral portions of the aortic cusps, and also of the commissural extremities, revealed no evidence of syphilis or rheumatic disease. In some places the syphilitic lesion in the aorta extended as far as the ring of the aortic valve, but the ring itself was not involved. Sections of the posterior mitral leaflet, the anterior and posterior tricuspid leaflets, the pulmonary valve, the ventricles, and the left atrium showed no conclusive evidence of rheumatic heart disease. There was extensive disease of the basal third of the anterior mitral leaflet, involving the myocardial fibrous boundary, the intervalvular fibrosa, and the subvalvular endocardium of the aortic valve. This entire region revealed marked, recent fibrosis, extensive vascularization, and exudation of lymphocytes and monocytes. In the tricuspid septal leaflet there were subacute inflammation and abscess formation in the ring and subvalvular endocardium. However, the free portion of the leaflet revealed no change except slight exudation of polymorphonuclear leucocytes at the base of the vegetations. The vegetations consisted of necrotic, eosinophilic material which contained many polymorphonuclear leucocytes and colonies of bacteria. Some lesions, especially in the aortic mitral leaflet, showed organization at their base.

Case 3.—A 58-year-old Negro was admitted to the hospital May 10, 1934, and died May 16, 1934. He complained of pain in the chest and fever of two weeks' duration. There was no history of syphilis. He had had three attacks of acute rheumatic fever, the first at the age of 10 years. The heart was enlarged, and a systolic and diastolic murmur was heard over the precordium. The blood pressure was 155/45. There were remittent fever, anemia, microscopic hematuria, conjunctival petechiae, and evidence of embolism of the left foot and arm. The spleen was not palpable. The blood Wassermann was strongly positive (four plus). A Type IV pneumococcus was recovered from the blood stream and from the sputum. The clinical diagnoses were acute bacterial endocarditis of the aortic valve, engrafted on syphilitic valvulitis, pneumococcus septicemia, bronchopneumonia, and congestive heart failure.

The main diagnoses at autopsy were acute bacterial endocarditis involving the aortic and mitral valves and the endocardium of the left ventricle; syphilitic aortitis; rheumatic heart disease, with chronic aortic and mitral valvulitis and chronic endocarditis of the left atrium; cardiac hypertrophy and dilatation (530 Gm.); recent infarcts of the spleen and left kidney; and bronchopneumonia. Culture of a vegetation yielded a Gram-positive diplococcus which was not isolated; culture of the heart's blood showed *Staphylococcus aureus.*

The root of the aorta revealed intimal wrinkling and scarring which were typical of syphilis, but the lesion did not extend into the aortic valve. This valve was the seat of rheumatic disease. The left and posterior cusps were adherent and showed diffuse thickening and retraction adjacent to the commissural raphe. The left-right and the right-posterior commissures were normal. There were thickening and slight nodularity of the left atrial endocardium above the posterior mitral leaflet. The mitral valve showed thickening along the line of closure, but the tricuspid and pulmonary valves were grossly negative.

The right and left aortic cusps were destroyed largely by friable, grayish-red vegetations. These extended from the free margin to the base and down over the endocardium below the right cusp, where there was slight penetration of the membranous portion of the interventricular septum. Vegetations were also attached to several chordae tendineae near the free margin of the anterior mitral leaflet.

The only microscopic sections available were several from the ventricles and one from the aortic valve. The myocardium showed slight perivascular fibrosis, subacute myocarditis, and focal abscesses. The aortic valve was destroyed completely and had been replaced by irregular masses of necrotic fibrin containing numerous polymorphonuclear leucocytes and colonies of bacteria. There was no organization of these lesions.

CASE 4.—A 45-year-old white man was admitted to the hospital Feb. 13, 1935, and died March 11, 1935. On admission he complained of cough, fever, and swelling of the ankles of four weeks' duration. He had a chancre at the age of 20, but there was no history of rheumatic fever. The heart was enlarged, and there were systolic and diastolic murmurs over the aortic area. The blood pressure was 130/80. The patient had fever and microscopic hematuria, but there were no anemia, petechiae, or emboli. The spleen was not palpable. Five blood cultures were negative. The blood and spinal fluid Wassermann reactions were positive. The clinical diagnoses were syphilitic heart disease, with aortic insufficiency, tabes dorsalis, and congestive heart failure.

The diagnoses at autopsy were endocarditis lenta involving the aortic and mitral valves, syphilis of the aorta and of the aortic valve, chronic rheumatic mitral valvulitis, cardiac hypertrophy and dilatation (450 Gm.), tabes dorsalis, chronic passive hyperemia of the viscera, and bronchopneumonia. Cultures of the heart's blood and of a vegetation showed no growth. Bacterial stains of a vegetation revealed Gram-positive cocci.

The root of the aorta revealed a typical syphilitic lesion involving the aortic valve in the region of the right-posterior commissure. At this site the right and posterior cusps were thickened and retracted and the commissure was slightly widened. The rest of the aortic valve showed no significant change. Both mitral leaflets were the seat of marked, diffuse thickening, and there were shortening, thickening, and adhesion of the chordae tendineae. The tricuspid and pulmonary valves and the left atrium were not diseased. Many small, friable, grayish-brown vegetations were attached to the ventricular aspect of the line of closure and midportion of all the aortic cusps, and also to the line of closure and free margin of the mitral leaflet and several chordae tendineae below the free margin.

Microscopically, the lateral extremities of the right and posterior aortic cusps adjacent to the right-posterior commissure revealed syphilitic involvement of the ring, with inflammation and scarring. In the free portion the only change was marked hyaline fibrosis. Numerous sections of the lateral and central segments of the cusps showed slight fibrosis, but no vascularity or exudation. In the myocardium there were perivascular fibrosis, subacute inflammation, and several typical Aschoff bodies. The mitral leaflets showed fibrosis, many lymphocytes and plasma cells, and diffuse vascularity with capillaries, arterioles, and thick-walled, small arteries. No significant change was present in the tricuspid or pulmonary valve, or in the left atrium. The vegetations consisted of necrotic fibrin, groups of polymorphonuclear leucocytes, and superficial colonies of bacteria. Slight organization was present at the base.

CASE 5.—A 44-year-old colored woman was admitted to the hospital Dec. 19, 1940, and died Dec. 29, 1940. She complained of shortness of breath of six months' duration. A diagnosis of aortic insufficiency had been made in 1931. There was no history of syphilis. She had had rheumatic fever at the age of 14. Physical examination revealed an enlarged heart, with systolic and diastolic murmurs over the aortic area. The blood pressure was 150/30. The patient showed slight fever, anemia, microscopic hematuria, and a strongly positive blood Wassermann reaction. There were no petechiae or emboli, and the spleen was not palpable. No blood cultures were made. The clinical diagnoses were syphilitic heart disease, with aortic insufficiency. Death was caused by acute pulmonary edema.

Fig. 4.—Case 5. Combined syphilitic and rheumatic disease of the aortic valve, with endocarditis lenta, in a 44-year-old colored woman. There are extensive vegetations in the region of commissure *B*. The aortic cusps are thickened and retracted, and there is commissural separation. The rheumatic lesion was established microscopically.

The diagnoses at autopsy were endocarditis lenta involving the aortic, mitral, and tricuspid valves and the intima of the root of the aorta; syphilis of the aorta and syphilitic aortic valvulitis, with insufficiency; rheumatic heart disease, with chronic aortic, mitral, and tricuspid valvulitis; cardiac hypertrophy and dilatation (450 Gm.); remote infarct of the left kidney; ascites; edema of the lower extremities; and bronchopneumonia. Culture of the heart's blood showed no growth. Culture of a vegetation on the aortic valve yielded *Streptococcus alpha.*

There was a diffuse syphilitic lesion of the root of the aorta, with extension into the aortic valve. The aortic cusps were thickened and retracted, especially at the commissural extremities, and all three commissures were widened (Fig. 4). Whether

or not there was rheumatic disease of the aortic valve could not be ascertained grossly because of the marked syphilitic lesion. The mitral, tricuspid, and pulmonary valves and the left atrium showed no evidence of rheumatic disease. There were large, friable, grayish-red vegetations on the ventricular aspect of all the aortic cusps, especially the right and posterior cusps. Vegetations were also attached to

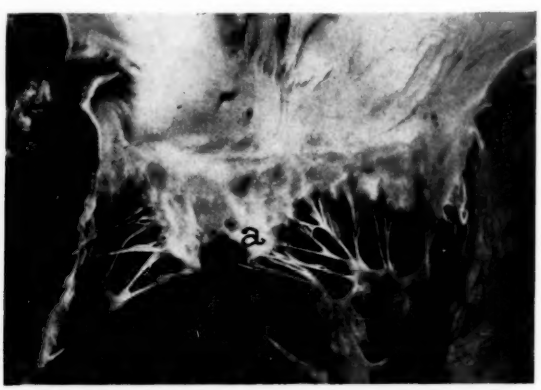

Fig. 5.—The mitral valve in Case 5. The anterior leaflet shows a single large vegetation at the line of closure. No conclusive evidence of rheumatic disease is present in the gross, although microscopic section (Fig. 6) revealed typical chronic valvulitis.

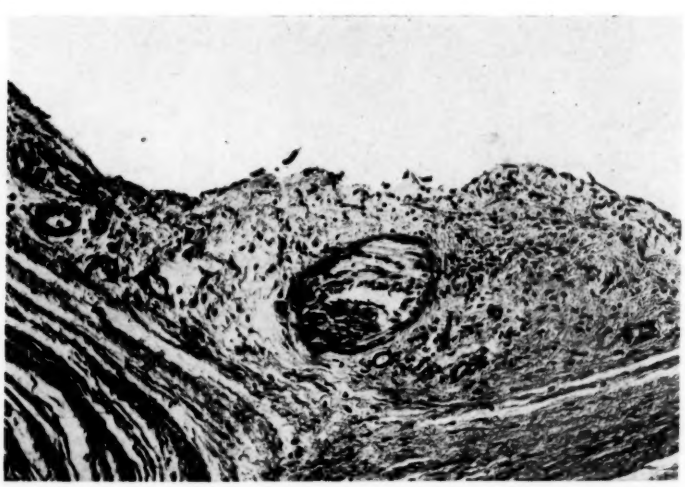

Fig. 6.—Case 5. Microscopic section of the posterior mitral leaflet at the line of closure (hematoxylin and eosin, ×130). There are fibrosis, vascularity with arterioles and thick-walled small arteries, and lymphocytic exudate.

the endocardium of the left ventricle below the aortic valve, where they penetrated the membranous portion of the interventricular septum and projected into the right ventricle in the region of the septal anterior commissure. Several vegetations were present on the line of closure of the tricuspid septal leaflet. A single large vegetation was attached to the atrial aspect of the line of closure of the anterior mitral leaflet, and there were smaller lesions on the adjacent chordae tendineae (Fig. 5).

Microscopically, the commissural extremities of the aortic cusps showed a syphilitic lesion of the ring and basal free portion, consisting of irregular hyaline

fibrosis and vascularization with capillaries and arterioles. The central portions of the cusps were not involved by syphilis; however, they showed diffuse change, chiefly in the ring spongiosa and ventricularis layer, consisting of fibrosis, vascularization to the line of closure with various types of vessels, including thick-walled small arteries, and focal lymphocytic exudate. The mitral valve (Fig. 6), and also the tricuspid to a less marked degree, revealed vascularity and chronic inflammation in the ring and free portion. The pulmonary valve and the left atrium showed no significant lesion. In the myocardium there were tiny focal abscesses, subacute inflammation, and suggestive, but not typical, Aschoff bodies. The vegetations consisted of masses of necrotic amorphous material, containing polymorphonuclear leucocytes and superficial colonies of bacteria. There was slight proliferation of fibroblasts at the base. Tiny vegetations, which had not been apparent grossly, were present on the intimal surface of the aorta in the sinus of Valsalva.

SUMMARY OF CASES

A summary of the clinical and pathologic data is presented in Tables I and II. Four of the patients were males and one was a female; three were negroes and two were white; and the ages ranged from 44 to 58 years. Three patients gave a history of a primary syphilitic lesion, and two others had a history of acute rheumatic fever. On physical examination all presented the typical signs of aortic regurgitation. The blood Wassermann reaction was positive in all cases. The duration of the illness ranged from three weeks to fourteen months. There were positive blood cultures in two cases.

A clinical diagnosis of syphilitic heart disease was made in four cases because of the history, positive Wassermann reaction, and signs of aortic insufficiency. Evidence of central nervous system syphilis was present in one case. In Case 2 the aortic regurgitation was attributed to bacterial endocarditis. In one instance (Case 5) a diagnosis of syphilitic aortic regurgitation was made nine years prior to the onset of the bacterial lesion. Bacterial endocarditis was diagnosed clinically in only two cases, and both were of the acute type. In two instances (Cases 1 and 5) there were no signs or symptoms indicative of bacterial endocarditis, and therefore the presence of the disease was not suspected during life. The presence of rheumatic heart disease was not detected clinically in any of the cases, either because the lesions were obscured by the syphilis or because they were of a slight and nondeforming nature.

Syphilis of the root of the aorta was present in all cases, and in three instances there was extension into the aortic valve. Unequivocal evidence of rheumatic heart disease was found in four cases, and in one instance (Case 2) there were suggestive, but not conclusive, lesions in the mitral and tricuspid valves. Aschoff bodies were present in the myocardium in one case. A combined syphilitic and rheumatic lesion of the aortic valve was demonstrated in two cases and probably was

TABLE I

CLINICAL DATA IN CASES OF SYPHILIS, RHEUMATIC FEVER, AND BACTERIAL ENDOCARDITIS*

CASE	AGE (YR.)	SEX	RACE	DURATION OF ILLNESS	HISTORY OF SYPHILIS	HISTORY OF RHEUMATIC FEVER	CARDIAC FINDINGS	WASSERMANN	BLOOD CULTURES	CLINICAL DIAGNOSES
1	55	M.	White	14 months	Primary lesion	None	Aortic regurgitation	4 plus	None made	Syphilitic heart disease, with aortic insufficiency
2	47	M.	Negro	9 weeks	Primary lesion	None	Aortic regurgitation	4 plus	*Streptococcus alpha*	Acute bacterial endocarditis of aortic valve, with insufficiency; tertiary syphilis
3	58	M.	Negro	3 weeks	None	3 attacks, first at 10 years	Aortic regurgitation	4 plus	Pneumococcus Type IV	Acute bacterial endocarditis engrafted on syphilitic aortic valvulitis; bronchopneumonia; pneumococcus septicemia
4	45	M.	White	2 months	Primary lesion	None	Aortic regurgitation	4 plus	Five negative cultures	Syphilitic heart disease, with aortic insufficiency
5	44	F.	Negro	6.5 months	None	1 attack at age of 14 years	Aortic regurgitation	4 plus	None made	Syphilitic heart disease, with aortic insufficiency

*Although rheumatic fever was not established in Case 2, it is included in the table for convenience.

present in a third (Case 4). The distribution of the bacterial vegetations is shown in Table II. The aortic and mitral valves were involved in every case, and in four instances the mitral lesions may have resulted from apposition with the aortic valve.

TABLE II

ANATOMIC DISTRIBUTION OF LESIONS IN CASES OF CARDIOVASCULAR SYPHILIS, RHEUMATIC HEART DISEASE, AND BACTERIAL ENDOCARDITIS

CASE	SYPHILIS	RHEUMATIC HEART DISEASE		BACTERIAL ENDOCARDITIS
		GROSS LESIONS	MICROSCOPIC LESIONS	
1	Root of aorta and aortic valve	Aortic valve	Aortic and mitral valves	Aortic and mitral valves
2	Root of aorta	None	None	Aortic, mitral, and tricuspid valves; endocardium of left ventricle
3	Root of aorta	Aortic and mitral valves; left atrium	Sections not available	Aortic and mitral valves; endocardium of left ventricle
4	Root of aorta and aortic valve	Mitral valve	Mitral valve; Aschoff bodies in left ventricle	Aortic and mitral valves
5	Root of aorta and aortic valve	None	Aortic, mitral, and tricuspid valves	Aortic, mitral, and tricuspid valves; intima of root of aorta

COMMENT

Table III presents data pertaining to the incidence of combined syphilitic heart disease and bacterial endocarditis in autopsy material. The total number of cases of bacterial endocarditis and also the number among these in which there were syphilitic aortitis and syphilis of the aorta and aortic valve are given. The figures generally indicate that association of the two diseases is infrequent or rare, but this is contrary to the experience of Braunstein and Townsend[1] and Wright and Zeek,[2] who found a much higher incidence. Apparently the combination of bacterial endocarditis and syphilitic aortitis alone occurs with approximately the same frequency as bacterial endocarditis and syphilitic aortitis with involvement of the aortic valve.

It generally is agreed that syphilitic aortitis alone does not predispose the aortic valve to the development of bacterial endocarditis.[2-4, 7] The association of a syphilitic lesion confined to the root of the aorta and bacterial vegetations of the aortic valve is in all probability merely coincidental. In such cases there is either an underlying nonsyphilitic valvulitis, chiefly rheumatic, or the bacterial lesion, especially if it is acute, is superimposed on a normal aortic valve. The latter probably holds for Case 2 of the present study. In cases of combined syphilitic

disease and bacterial endocarditis of the aortic valve, syphilis can be considered a predisposing factor only after excluding rheumatic heart disease, for the latter is the usual precursor of bacterial endocarditis. This requires careful examination of both the aortic valve and the rest of the heart for rheumatic stigmata.

TABLE III

INCIDENCE OF COMBINED SYPHILITIC HEART DISEASE AND BACTERIAL ENDOCARDITIS IN AUTOPSY MATERIAL

YEAR	INSTITUTION	OBSERVER	NO. OF CASES OF BACTERIAL ENDOCARDITIS*	CASES OF SYPHILIS OF AORTA†		CASES OF SYPHILIS OF AORTA AND AORTIC VALVE	
				NO.	%	NO.	%
1926	Johns Hopkins	Thayer[4]	130			2	1.5
1937	Mt. Sinai	Gross and Fried[5]	70			1	1.4
1938	Los Angeles County	Martin and Adams[6]	157	5	3.2	2	1.3
1940	Baltimore City	Braunstein and Townsend[1]	58			9	15.5
1940	Cincinnati General	Wright and Zeek[2]	84	18	21.4	10	12.0
1940	Michael Reese and Cook County	Rosenberg[3]	273	19	7.0	7	2.6
1942	Institute of Pathology, University Hospitals of Cleveland	Koletsky	80	5	6.3	3	3.8

*The figures represent the total number of cases of bacterial endocarditis, not merely those of involvement of the aortic valve. Both subacute and acute forms are included.

†The figures represent the total number of cases of syphilitic aortitis, both with and without involvement of the aortic valve.

A rheumatic lesion of the aortic valve may be obscured in the presence of syphilis and hence may be difficult or impossible to detect grossly. This is especially true when the valve is the seat of extensive syphilis, with thickening and commissural separation of cusps and only minimal rheumatic disease. The identification of a well-developed rheumatic lesion is comparatively simple when the syphilis is slight. Submarginal adhesions of adjacent cusps, or fusion, with the formation of a commissural raphe, are presumptive evidence of rheumatic heart disease, for syphilis rarely, if ever, produces such deformities. Other indications of the presence of rheumatic heart disease are marked thickening and retraction in the central and lateral portions of the cusps, with only slight involvement of the commissural extremities.

A microscopic diagnosis of rheumatic involvement of the aortic valve often can be established in the presence of syphilis because the two lesions differ in type and distribution.[9] The syphilitic change[8, 9] is

confined largely to the commissural extremities of the cusps, and, since these are involved by direct extension from the aorta, the inflammation and scarring are marked in the ring and base of the cusp and diminish as the free margin is approached. The midportions of the cusps may be the seat of fibrosis, but, even when the lesion is extensive, they show no vascularity or significant exudate. Direct extension of syphilis from the aorta into the central portions of the cusps, i.e., the so-called ascending type of lesion, is uncommon, and, when present, the inflammation is largely limited to the ring. In contrast, well-developed rheumatic fever produces a more or less diffuse valvulitis and can thus be recognized by characteristic inflammatory changes in the central and lateral regions of the cusps, where there is no significant overlapping with syphilis. Vascularization, exudation, and fibrosis are present both in the ring and free portion of the cusps, chiefly in the ventricularis layer, and may extend to the line of closure. The commissural raphe of rheumatic fever is distinctive and readily identified microscopically. There is diffuse hyaline fibrosis, but vascularity and inflammation usually are confined to the distal and basal portion of the ridge, just above the subaortic angle.

In some instances of slight rheumatic involvement of the aortic valve, however, positive identification of the lesion is difficult. The microscopic observations in such cases are often equivocal, especially with respect to the presence of significant vascularity and fibrosis in the free portions of the cusps. The diagnosis of rheumatic heart disease then depends upon the recognition of stigmata of rheumatic fever elsewhere in the heart. These are especially common in the mitral and tricuspid valves, where they are easily recognized. The gross stigmata include thickening of the mitral, tricuspid, and pulmonary valves, particularly along the line of closure and free margin; thickening, shortening, and adhesion of the chordae tendineae; irregular thickening and wrinkling of the left atrial endocardium above the posterior mitral leaflet; and fibrous pericardial adhesions, especially in the atrioventricular sulci. Characteristic microscopic lesions consist of vascularity, fibrosis, and exudate in the ring and free portions of the mitral, tricuspid, and pulmonary valves; vascularity and reduplication of the elastica of the endocardium of the left atrium; and Aschoff bodies in the myocardium. These stigmata cannot be confused with syphilis, for the latter is practically confined to the aortic valve. Whether the rare cases[10, 11] of alleged syphilitic stricture of the mitral valve are authentic is open to doubt. Very rarely the syphilitic lesion of the aortic valve spreads down into the membranous portion of the interventricular septum and anterior mitral leaflet. Three such cases have been described.[12, 13] In all of these, however, there was gummatous necrosis of the anterior mitral leaflet, and this, together with the demonstration of extension from the aortic valve,

would readily distinguish the lesion from that caused by rheumatic fever.

There were three cases of syphilitic aortic valvulitis in this study; a rheumatic lesion of the aortic valve was demonstrated grossly in one, and microscopically in another. There were two additional cases of syphilitic aortitis, and gross rheumatic disease of the aortic valve was observed in one. However, unequivocal rheumatic stigmata were identified in other parts of the heart in four cases, and in two instances the lesions were entirely microscopic. This indicates the importance of complete microscopic study when no conclusive evidence of rheumatic disease is present grossly. Blocks should be made according to the method of Gross, Antopol, and Sacks.[14] Even multiple sections of the valves, especially the mitral and tricuspid, are of value in some cases, for the first section may be equivocal or negative, whereas, in additional sections, the signs of inflammation are plainly evident.

Until 1940, only a small number of cases of coexisting syphilitic aortic valvulitis and bacterial endocarditis had been reported. Of these, Braunstein and Townsend,[1] Wright and Zeek,[2] and Rosenberg[3] accept, as authentic, eleven, six, and nine cases, respectively. A summary of the latter has appeared in their papers[1-3] and need not be presented here. However, a review of the cases reveals that in most instances the diagnoses were based on gross observation; microscopic study was entirely lacking or inadequate. This would result in the recognition of pronounced rheumatic lesions, but slight disease may have been overlooked. Moreover, in some instances, the mitral and tricuspid valves showed vegetations which did not appear to be the result of apposition with the aortic valve, and these may have been engrafted on rheumatic disease. Since rheumatic heart disease was not satisfactorily excluded, very few, if any, of these cases should be accepted as authentic instances of bacterial endocarditis superimposed on a syphilitic lesion.

In 1940 there were several reports dealing with coexisting syphilis and bacterial endocarditis of the aortic valve, and all presented similar conclusions. Wright and Zeek[2] described five cases, which constituted 7 per cent of sixty-eight autopsy cases of syphilitic aortic valvulitis at the Cincinnati General Hospital and concluded that syphilis of the aortic valve was an important precursor of bacterial endocarditis. Braunstein and Townsend[1] reported nine cases, which represented 3.3 per cent of 267 cases of syphilitic aortic valvulitis from among 4,921 consecutive autopsies at the Baltimore City Hospital. This incidence was held to indicate that the combination of bacterial endocarditis and syphilitic aortic valvulitis was more common than is generally stated. A similar conclusion was reached by Rosenberg,[3] who described seven autopsy cases of syphilis and bacterial endocarditis of the aortic valve from the Michael Reese and Cook County Hospitals.

In two of these reports[2, 3] the authors stated that the presence of rheumatic lesions was excluded in their cases. However, no mention was made of any investigation of the aortic valve to rule out an obscure rheumatic lesion, or of complete microscopic examination of other valves for rheumatic stigmata. The conclusion that syphilitic aortic valvulitis not infrequently acts as a precursor of bacterial endocarditis is at variance with the older belief[4, 15] that this combination is extremely rare. In our experience the association of cardiovascular syphilis and bacterial endocarditis has been infrequent, rather than rare, and largely confined to hearts which were the seat of rheumatic disease. There were rheumatic stigmata in five of the ten cases of syphilitic aortic valvulitis and bacterial endocarditis studied by Wright and Zeek.[2] It is clear that hearts with a combined syphilitic and bacterial lesion may harbor rheumatic disease and that the latter, especially if it is slight, will be overlooked when the examination of the heart is incomplete.

Only scant data are available on the frequency of combined cardiovascular syphilis and rheumatic heart disease. Among 1,031 autopsies at City Hospital, Welfare Island, Lisa and Chandlee[16] encountered seventy-one cases of syphilitic heart disease, exclusive of aneurysm, and in eight, or 12 per cent, of these, there were also rheumatic lesions. Swanson[17] found four instances (7 per cent) of syphilitic aortitis associated with rheumatic heart disease among fifty-seven cases of cardiovascular syphilis of all types in 1,841 autopsies at the Vanderbilt Hospital. However, very few cases of combined syphilitic and rheumatic disease of the aortic valve, established by autopsy, have been reported. There was one in the group described by Lisa and Chandlee,[16] and Sager and Sohval[9] reported three cases in 1934. The figures on combined syphilitic and rheumatic heart disease at the Institute of Pathology of the University Hospitals of Cleveland are of interest. Among 4,000 consecutive autopsies from May, 1930, to May, 1941, there were 135 cases of cardiovascular syphilis, and in twenty-four, or 18 per cent, of these, a diagnosis of rheumatic heart disease was also made. Over the same period, there were 475 cases of rheumatic heart disease and eighty cases of bacterial endocarditis. In four cases there was combined syphilitic and rheumatic disease of the aortic valve. Of the twenty-three hearts which were the seat of both syphilis and rheumatic fever, four, described in this paper, also revealed evidence of bacterial endocarditis.

That bacterial endocarditis is engrafted with far greater frequency on rheumatic than on syphilitic lesions is an established fact. The reasons for this have been largely speculative. The difference in the behavior of these lesions toward bacterial endocarditis is too great to be explained merely by a difference in incidence of cardiovascular syphilis and rheumatic heart disease in various localities.[2] Nor is the suggestion tenable that the rare association of syphilis and bacterial endocarditis is due to the fact that the latter is essentially a disease of younger persons,

whereas cardiovascular syphilis affects an older group.[18] Several morphologic explanations have been offered. One is that the rheumatic valve has greater vascularity than the syphilitic and is thus more likely to become the seat of bacterial invasion. This concept depends upon the theory of embolic origin of endocarditis, which appears not to be generally applicable.[5, 19, 20] Moreover, bacterial endocarditis is frequently superimposed on slight or mild rheumatic lesions which are poorly vascularized. Saphir and Wile[21] suggest that in syphilis the excursion of the aortic cusps is limited, so that only a small area for the settling of bacteria is available. In nonsyphilitic valvulitis, on the other hand, shortening of the cusps in their longitudinal diameter and adhesions at the commissures provide larger than normal areas for bacterial implantation. At present most observers believe that bacterial endocarditis arises chiefly as a surface infection of valves whose damaged endocardium provides an anchoring ground for bacteria.[5, 19, 20] Suitable endocardial changes of degenerative, inflammatory, and thrombotic types are more frequent in rheumatic fever than in syphilis. For example, Grant, Wood, and Jones[19] found that platelet thrombi, which provide a nidus for localization and growth of bacteria, are common in rheumatic valvular disease and infrequent in syphilis.

SUMMARY AND CONCLUSIONS

Among 4,000 consecutive autopsies at the Institute of Pathology of the University Hospitals of Cleveland there were five cases of combined syphilitic heart disease and bacterial endocarditis. In two there was syphilitic aortitis alone, and in three there was also involvement of the aortic valve. In no case could significance be attached to the syphilitic lesion as a precursor of bacterial endocarditis. Stigmata of rheumatic fever were demonstrated unequivocally in four cases, and in at least two of these there was a combined syphilitic and rheumatic lesion of the aortic valve. In the fifth case the syphilis was confined to the root of the aorta, and the acute bacterial endocarditis was apparently superimposed on a normal aortic valve. These observations lend no support to the belief that syphilis is a significant predisposing factor in the development of bacterial endocarditis. Hearts with lesions of both syphilis and bacterial endocarditis should be subjected to thorough examination for stigmata of rheumatic fever.

REFERENCES

1. Braunstein, A. L., and Townsend, S. R.: Bacterial Endocarditis Superimposed on Syphilitic Aortic Valvulitis, Arch. Int. Med. **65**: 937, 1940.
2. Wright, J., and Zeek, P. M.: Bacterial Endocarditis Superimposed on Syphilitic Aortic Valvulitis, Am. Heart J. **19**: 587, 1940.
3. Rosenberg, D. H.: Bacterial Endocarditis and Syphilis of the Aortic Valve, Arch. Int. Med. **66**: 441, 1940.
4. Thayer, W. S.: Studies on Bacterial (Infective) Endocarditis, Johns Hopkins Hosp. Rep. **22**: 1, 1926.

5. Gross, L., and Fried, D. M.: The Role Played by Rheumatic Fever in the Implantation of Bacterial Endocarditis, Am. J. Path. **13**: 769, 1937.
6. Martin, H. E., and Adams, W. L., Jr.: Bacterial Endocarditis Superimposed on Syphilitic Aortitis and Valvulitis. A Clinicopathological Study With 5 Case Reports, AM. HEART J. **16**: 714, 1938.
7. Smith, F. J.: The Co-existence of Syphilis of the Aorta and Bacterial Endocarditis, Internat. Clin. **2**: 1, 1937.
8. Saphir, O., and Scott, R. W.: The Involvement of the Aortic Valve in Syphilitic Aortitis, Am. J. Path. **3**: 527, 1927.
9. Sager, R. V., and Sohval, A. R.: Combined Syphilitic and Rheumatic Disease of the Aortic Valve. Report of Three Cases, Arch. Path. **17**: 729, 1934.
10. Lutembacher, R.: Lesions mitrales et syphilis, Presse méd. **43**: 1830, 1935.
11. Raynaud, R., Marill, F. G., and d'Eshougues, J. R.: Le rétrécissement mitral syphilitique, Presse méd. **47**: 627, 1939.
12. Staemmler, M.: Ueber Syphilis der Mitralis, Verhandl. d. deutsch. path. Gesellsch. **25**: 262, 1930.
13. Blackman, S. S.: Syphilis of Mitral Valve and Membranous Interventricular Septum of Heart, Bull. Johns Hopkins Hosp. **57**: 111, 1935.
14. Gross, L., Antopol, W., and Sacks, B.: A Standardized Procedure Suggested for Microscopic Studies on the Heart, With Observations on Rheumatic Hearts, Arch. Path. **10**: 840, 1930.
15. Libman, E.: Affections of Heart Valves, M. Clin. North America **1**: 573, 1917.
16. Lisa, J. R., and Chandlee, G. J.: The Heart and Great Vessels in Combined Syphilitic and Rheumatic Infection, Arch. Int. Med. **54**: 952, 1934.
17. Swanson, H.: Combined Syphilitic Aortitis and Rheumatic Disease of the Heart, AM. HEART J. **18**: 672, 1939.
18. Briggs, L. H.: Bacterial Endocarditis as a Sequel to Syphilitic Valve Defect, Am. J. M. Sc. **164**: 275, 1922.
19. Grant, R. T., Wood, J. E., and Jones, T. D.: Heart Valve Irregularities in Relation to Subacute Bacterial Endocarditis, Heart **14**: 247, 1928.
20. Keefer, C. S.: Subacute Bacterial Endocarditis: Active Cases Without Bacteremia, Ann. Int. Med. **11**: 714, 1937.
21. Saphir, O., and Wile, S. A.: Rheumatic Manifestations in Subacute Bacterial Endocarditis in Children, AM. HEART J. **9**: 29, 1933.

LUMBAR SYMPATHECTOMY IN THE TREATMENT OF INTERMITTENT CLAUDICATION

Selection of Cases by Claudication Test With Lumbar Paravertebral Procaine Injection

Norman E. Freeman, M.D., and Hugh Montgomery, M.D.
Philadelphia, Pa.

INTERMITTENT claudication is caused by the pain which develops in working muscles in the absence of an adequate circulation. This condition is frequently encountered in patients with arterial occlusion and may be incapacitating. Two theories have been advanced to explain the reduction in circulation: first, that the diminished blood flow is caused by spasm of the blood vessels supplying the muscles; second, that the organic obstruction of the arteries prevents adequate circulation. Both theories maintain, however, that the pain which causes intermittent claudication ultimately derives from a reduction in blood flow through muscles. For a discussion of the mechanism of the pain associated with intermittent claudication, reference is made to the work of Lewis, Pickering, and Rothschild,[1] and Veal and McFetridge.[2]

In the treatment of intermittent claudication, lumbar sympathectomy has been considered ineffective as a means of increasing the blood supply to the muscles of the leg. Homans,[3] in his recent monograph on peripheral vascular disease, stated: "As a cure for intermittent limp, lumbar sympathectomy is not recommended." Landis and Montgomery[4] believed that intermittent claudication was "not affected" by sympathectomy. On the other hand, the following observers have reported cases in which there was considerable relief from claudication after excision or paralysis of the lumbar sympathetic nerves: Brown,[5] Flothow,[6] Morton and Scott,[7] Reichert,[8] Telford,[9] Harris,[10] White,[11] Davis,[12] and Pearl.[13] The improvement consisted of relief of pain and an increase in the "walking distance." No objective evidence that there is an increase in the blood supply to the muscles after sympathectomy has been presented. On the other hand, physiologic observations by Grant and Pearson,[14] Holling,[15] Kunkel, Stead, and Weiss,[16] and Abram-

From the Peripheral Vascular Clinic of the Robinette Foundation, the Harrison Department of Surgical Research, and the Graduate Hospital of the University of Pennsylvania, Philadelphia.

Read before the Philadelphia Academy of Surgery, Dec. 2, 1940.

Presented at the Seventeenth Meeting of the American Heart Association, Cleveland, Ohio, May 31, 1941.

Received for publication Aug. 29, 1941.

son and Ferris[17] have shown in normal human subjects that the blood flow through muscle is actually increased by sympathetic stimulation.

It was therefore felt that some objective method of estimating the severity of intermittent claudication should be used in a study of the benefits to be obtained from paralysis of the vasoconstrictor nerves. Such an objective method is furnished by the claudication test of Hitzrot, Naide, and Landis.[18]

White[19] was the first to suggest blocking the lumbar sympathetic nerves with procaine as a diagnostic procedure. Flothow[6] extended its use, and Reichert[8] actually employed it to evaluate the probable benefits to be derived from prolonged paralysis of the sympathetics with alcohol. Pearl[13] more recently has found it useful in his studies on claudication.

In this study we have measured the severity of intermittent claudication in twelve patients with obliterative vascular disease of the lower extremities, both before and after blocking the lumbar sympathetic ganglia with procaine. The results of the tests, as well as the effects of the subsequent sympathectomies on six of the patients, form the basis for the present communication.

The hypothesis which guided us in the selection of tests, in the interpretation of symptoms, and in planning treatment in the various cases may be stated as follows: In some cases of arterial occlusive disease there is apparently also an element of abnormal vasoconstriction which is superimposed upon the underlying condition and aggravates the circulatory deficiency. The mechanism by which the vasoconstriction aggravates the symptoms of arterial disease will be discussed later. Clinical signs which are interpreted as indicating abnormal vasoconstriction are (1) cyanosis of the feet, (2) increased sweating, and (3) constriction of the superficial veins of the feet and legs when the patients are subjected to the emotional stimulation of examination. Patients who present evidence of abnormal vasoconstriction and show improvement after lumbar paravertebral procaine injection may, we believe, be benefited by lumbar sympathectomy.

METHODS

1. Claudication Test.—The ability of the calf muscles to contract was studied by means of the claudication test described by Hitzrot, Naide, and Landis.[18] The amount of work which can be performed has been shown to depend upon the efficiency of the circulation. By this method, the muscles of the calf are stimulated at regular intervals by means of electrodes placed on the calf of the leg. Extension of the foot against a spring resistance is measured on a kymograph. The current is adjusted in such a way as to give good contraction of the muscles. Between 2.2 and 3.8 amperes were found to be necessary. The same strength of current was used before and after paravertebral injection on all except one of the patients. We chose to use stimuli at the rate of one every two seconds for two minutes. The patients were then given one minute of rest, and the calf was

TABLE I

CASE	INITIALS	SEX	AGE (YR.)	DIAGNOSIS	MOST DISTAL PULSES PRESENT	CALCIFICATION OF ARTERIES OF LEGS	WALKING DISTANCE		CLAUDICATION TEST		MAXIMUM TEMPERATURE OF TOES AFTER INJECTION	GANGLIA REMOVED AT OPERATION	WALKING DISTANCE AFTER LUMBAR SYMPATHECTOMY
							BEFORE INJECTION	AFTER INJECTION	BEFORE INJECTION	AFTER INJECTION			
1	H. T.	M	67	Arteriosclerosis and vasoconstriction	Right and left femorals	+	1 block	2½ blocks	3.9	3.6	28.5	Right L 2, 3, 4 Left L 2, 3, 4	15 blocks
2	H. McC.	M	41	Vasoconstriction and obliteration	Right femoral and left dorsalis pedis	0	100 yards	500 yards	21.0	17.0	30.1	Left L 1, 2, 3	2 blocks. Limited by angina pectoris
3	T. D.	M	46	Vasoconstriction and obliteration	Right dorsalis pedis and left popliteal	+	1 block	4 blocks	11.5	15.9	33.1	Right L 1, 2, 3 Left L 1, 2, 3	Unlimited
4	J. L.	M	65	Vasoconstriction and obliteration	Right posterior tibial and left femoral	0	40 yards	150 yards	8.2	6.5	32.2		

5	J. C.	M	33	Thromboangiitis obliterans and vasoconstriction	Right femoral, left dorsalis pedis, and posterior tibial	0	1 block	1 block	6.8	7.5	29.1		
6	F. D.	F	52	Arteriosclerosis	No pulses palpable		½ block	½ block	5.8		29.5		
7	L. P.	F	40	Diabetes peripheral neuritis and vasoconstriction	Right and left posterior tibials		2 blocks	2 blocks	2.0	1.0	31.4		
8	A. S.	M	37	Thromboangiitis obliterans and vasoconstriction	Right and left femorals		1 block	4 blocks	11.5	12.4	30.1	Right L 1, 2, 3	8 blocks
9	A. N.	M	32	Thromboangiitis obliterans and vasoconstriction	Right femoral and left posterior tibial		1 block	4 blocks	9.0	14.1	30.6	Right L 1, 2	8 blocks
10	L. T.	M	42	Thromboangiitis obliterans and vasoconstriction	Right dorsalis pedis and left femoral	0	3 blocks	3 blocks	10.7	17.2	30.8		
11	C. K.	M	59	Vasoconstriction and obliteration	Right posterior tibial and left femoral	0	2 flights of stairs	5 flights of stairs	11.0	14.7	33.2		
12	A. M.	M	60	Vasoconstriction	Right dorsalis pedis, right posterior tibial, left dorsalis pedis, and left posterior tibial	0	2 blocks	8 blocks	10.0	14.0	32.2	Right L 1, 2, 3	Unlimited

stimulated once every second for two minutes. The time of onset of the pain was noted, and, for purposes of comparison (Table I), the average amplitude of contraction during the last ten seconds was taken.

2. Skin Temperature.—The skin temperature of the toes was measured by means of a thermocouple connected with a galvanometer. For purposes of record (Table I), the highest skin temperature which was observed after paravertebral procaine block was used.

3. Paravertebral Block.—With the patient lying on the normal side, three or four 22 gauge needles, 4 inches long, were inserted opposite the spinous processes of the lower thoracic and upper lumbar vertebrae at a distance of 4 to 6 cm. from the midline. The paths of the needles were infiltrated with a 1 per cent procaine solution which contained adrenalin (three drops of a 1:1,000 solution of adrenalin chloride to the ounce). At a distance of 3 cm. below the transverse processes in the lower thoracic, and 4 cm. in the lumbar, region, 5 c.c. of a 2 per cent procaine solution, with adrenalin, were injected after ascertaining that the tip of the needle was not in a blood vessel, in the pleura, or in the subarachnoid space. Within five to ten minutes, signs of sympathetic paralysis became evident, as shown by (a) dilatation of the superficial veins, (b) improvement in the color of the skin of the leg and foot, (c) absence of sweating, and (d) a rise in skin temperature of the toes of the injected side. When the skin temperature of the toes had reached a stationary level, and when other signs of sympathetic paralysis were present, the patient was placed in the dorsal position, and the claudication test was repeated, using the same strength of current and the same sequence of stimulation.

4. Walking Distance.—At the conclusion of the second claudication test the patient was allowed to sit up and then to walk at his customary pace. He was told to stop when the pain became so severe that he normally would have stopped walking.

5. Precautions.—The retroperitoneal and retropleural tissues are vascular, and absorption from these places takes place rapidly, possibly by way of the prevertebral veins described by Batson.[20] Several severe reactions were observed. In order to prevent the occurrence of reactions, 1.5 grains of sodium amytal were usually given before the test, and the procaine was injected *slowly*. Psoas weakness was produced occasionally by diffusion of the procaine through the substance of the muscle. This complication followed injections into the third and fourth paravertebral ganglia more frequently than injection into the upper lumbar and lower thoracic ganglia. This weakness was detected when the patient was allowed to sit up at the conclusion of the second claudication test.

6. Operations.—The extraperitoneal approach to the lumbar sympathetic ganglia was employed in all of the sympathectomies. This approach was first described by Royle,[21] in 1924. Flothow[22] suggested a muscle-splitting incision in 1935, and this operation was modified by Pearl,[23] in 1937. The aim of the sympathectomy in their cases was to relieve abnormal vasoconstriction in the feet. Full vasodilatation in this region is achieved by resection of the second, third, and fourth lumbar ganglia. Sweating and other evidences of sympathetic activity, however, generally persist above the ankle after this operation. In one of our earlier cases, even though 6.5 inches of the lumbar sympathetic chain were removed, sweating was still present down to the ankle on the medial side of the leg. We accordingly adopted Harris'[10] technique, and made a transverse subcostal incision. Particular efforts were made to extract the first lumbar ganglion from the substance of the diaphragm. Since then, in all of our patients, sweating has been absent below the knee.

RESULTS

All but one of the patients who were selected for study (Table I) presented evidence of abnormal vasoconstriction, as shown by cyanosis

of the feet, contracted veins (Fig. 1), and sweating under the emotional tension of examination. Ten of the patients showed either subjective or objective improvement after paravertebral procaine block. Fig. 2 shows the record of the claudication test which was done on one of these patients before and after the injection.

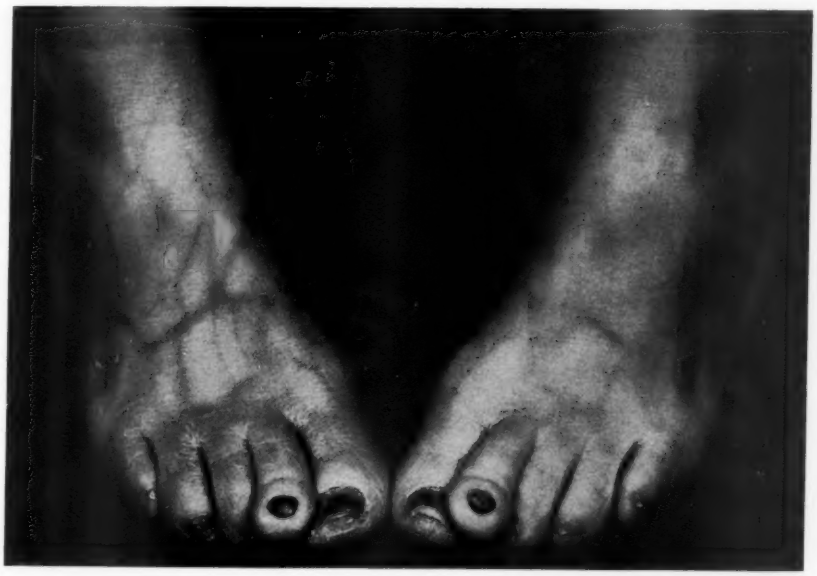

Fig. 1.—Infrared photograph of the feet (to show the prominence of the veins on the sympathectomized side. Patient A. M. (Table I, Case 12.)

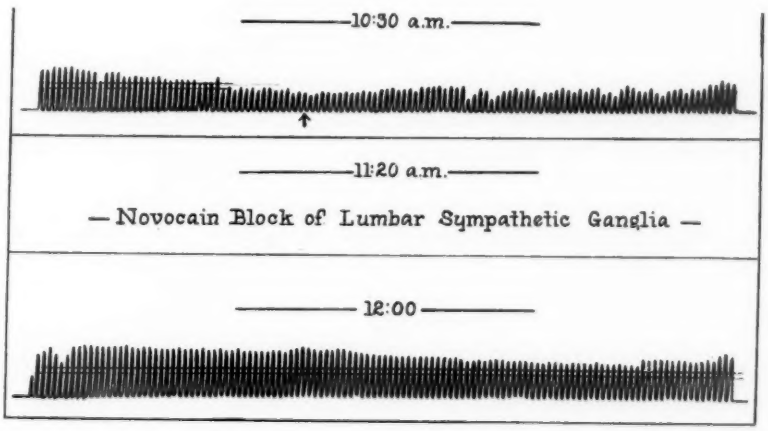

Fig. 2.—Claudication test before and after paravertebral injection of procaine in region of right lumbar sympathetic ganglia (first to fourth lumbar). Patient A. N. (Table I, Case 9.)

One patient with arteriosclerosis, and another with diabetes and peripheral neuritis, showed no improvement, as estimated either by the claudication test or the "walking distance" after the injection.

The temperature of the toes of all the patients who were tested showed a rise when the vasoconstrictor tone was removed. An example of the rise in skin temperature is shown in Fig. 3.

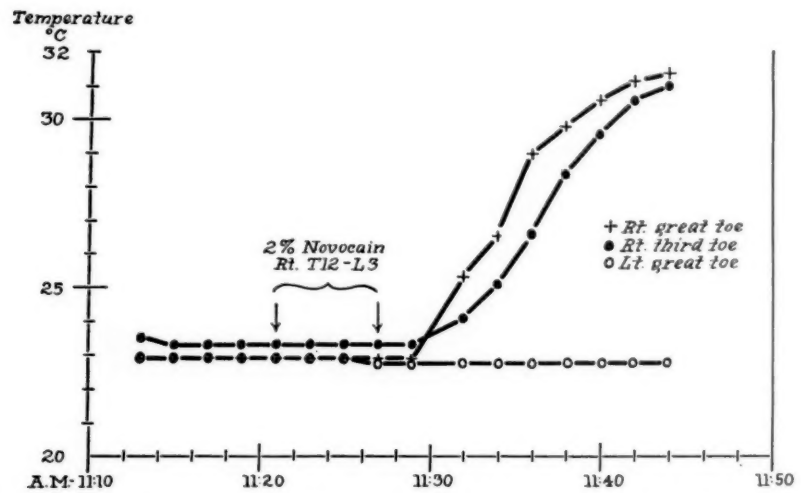

Fig. 3.—Increase in temperature of toes after paravertebral injection of right lumbar sympathetic ganglia. Patient A. N. (Table I, Case 9.)

Six of the ten patients who showed improvement in their ability to walk after paravertebral procaine block were subjected to lumbar sympathectomy, and in two of these cases a bilateral lumbar sympathectomy was performed. In all except one patient, the first, second, and third lumbar ganglia, with the intervening chain, were removed. In one patient with coexistent hypertension, the major and minor splanchnic nerves were also resected. All of the patients recovered from their operations without complications. Immediate and increasing lessening of the intermittent claudication was noted in five of the six patients on whom lumbar sympathectomy was performed.

DISCUSSION

Improvement in the ability of the calf muscles to perform work after paralysis of the vasoconstrictor nerves was demonstrated in seven patients. By means of the claudication test, we have, therefore, been able to obtain objective evidence which substantiates the hypothesis that vasoconstriction aggravates the circulatory defect produced by organic arterial obstruction.

The temporary relief from claudication after paravertebral procaine block and the persistent relief after lumbar sympathectomy confirm

the observations of many others who have studied the influence of sympathetic paralysis upon this condition. Our studies, like theirs, however, do not appear to be in harmony with the physiologic evidence that sympathetic stimulation influences blood flow through muscle. Hoskins, Gunning, and Berry[24] were the first to show in the experimental animal that sympathetic stimulation, although it caused vasoconstriction in the skin, produced vasodilatation in muscle. Recent work on man by Grant and Pearson,[14] Holling,[15] Kunkel, Stead, and Weiss,[16] and Abramson and Ferris[17] showed that the blood flow through resting human muscle was increased by sympathetic stimulation or by the intravenous injections of adrenalin. In an effort to harmonize our results with these physiologic observations, various factors will be considered.

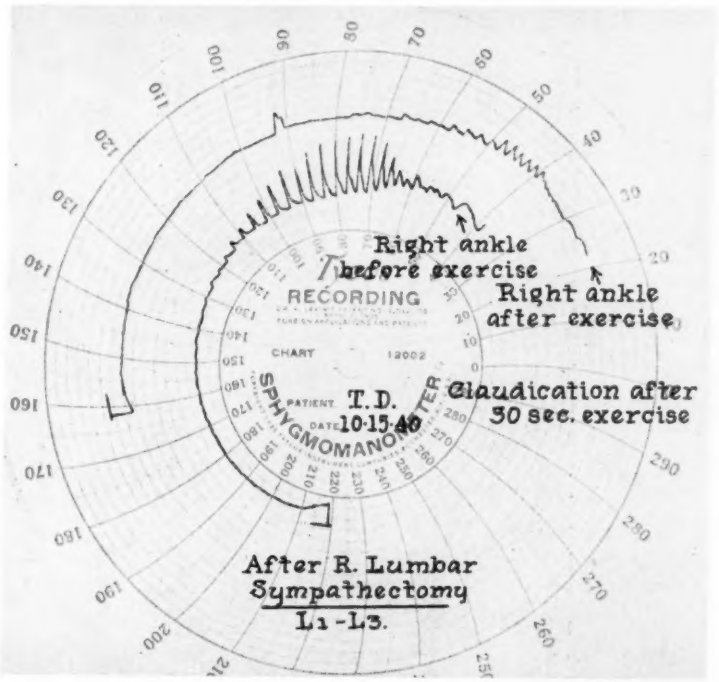

Fig. 4.—Oscillations at the ankle before and after the production of intermittent claudication in a sympathectomized limb. The oscillations just below the knee, but above the calf, were increased after the exercise. Patient T. D. (Table I, Case 3.)

It has been suggested that sympathectomy might interfere with the perception of pain from the blood vessels of the muscles (Leriche[25]). This explanation does not seem likely because the typical pain which induces intermittent claudication was produced in all of our patients, even after sympathectomy, by extending the period of exercise.

Another possibility is the fact that the blood vessels in all of our patients were abnormal, and might have gone into spasm under the ex-

perimental conditions. Pearl[13] has called attention to the clinical signs of vasospasm in the foot and ankle which were associated with the production of intermittent claudication in his cases. He has, in fact, suggested the term "angiospastic claudication" for this condition. He found that the dorsalis pedis pulse disappeared and the foot became blanched when claudication was produced by exercise, even though the pulse had been present and the foot was initially of good color. His observations appear to differ from those of Lewis, Pickering, and Rothschild[1] and Veal and McFetridge[2] on the behavior of the muscle vessels during the pain which causes intermittent claudication. These investigators found that during muscular activity associated with intermittent claudication there was actually an increase in the caliber of the muscle blood vessels, as shown both by blood flow studies and by arteriography. An explanation for Pearl's observations may be that the blood vessels of the calf were wide open as a result of the increased demand of muscular metabolism. In one of our patients, even though the leg was demonstrably sympathectomized below the knee, and, presumably, the ability of the vessels to go into spasm was lost, the foot became pale, the pulses diminished, and the oscillations at the ankle decreased after extended exercise (Fig. 4), whereas the oscillations just below the knee, but proximal to the calf, were actually increased. With the diversion of the available circulation into the dilated blood vessels of the calf, the blood flow to the foot and ankle and the pulsations of the vessels in this region were decreased.

A possible explanation for the beneficial effect of sympathectomy on intermittent claudication is suggested by the ingenious experiments of Roome,[26] who studied the effect of intra-arterial injections of adrenalin on the blood flow through muscle in the anesthetized dog. It is well known from the work of other investigators that a variable reaction is obtained—sometimes dilatation, sometimes constriction—when adrenalin is injected intra-arterially or intravenously. Roome found that the vascular reaction of muscle blood vessels to adrenalin was diphasic. By analyzing the time relationship of the vasomotor response in relation to the rate of flow, he came to the conclusion that the action of adrenalin, when injected intra-arterially, was to constrict the arteries and arterioles of the muscle, but at the same time to dilate the capillaries. The ultimate result on the blood flow depended upon the time at which the adrenalin came into contact with these vessels. With this concept in mind, it is possible to harmonize the reports on the influence of sympathetic stimulation on muscle blood flow with the beneficial results of sympathectomy in the treatment of intermittent claudication. It is quite probable that sympathetic stimulation dilates the muscle capillaries, but, at the same time, especially in patients with abnormal vasoconstriction, it probably constricts the arterioles and the arteries to such a degree as to interfere with the delivery of blood to those capillaries.

After the removal of arteriolar vasoconstrictor tone by sympathectomy, the maximum flow of blood allowed by the obstructed arteries is then available for capillary distribution.

There were two patients in this series (Cases 5 and 10) who showed evidence of objective improvement by the claudication test, and yet obtained no subjective relief after lumbar sympathetic block. Both of these patients were suffering from thromboangiitis obliterans, and it was our feeling that they probably had occlusion of the blood vessels supplying localized areas in the muscles and that it was the ischemia in these areas which was producing the symptoms. Even though paralysis of the vasoconstrictors brought about an increase in blood flow to the calf as a whole and resulted in an increase in the ability to perform work, the ischemia of the localized area was presumably not relieved, so that the symptoms persisted. Sympathectomy was not recommended in these cases.

There were three patients in this series (Cases 1, 2, and 4) who failed to show objective evidence of improvement, and yet obtained subjective relief after paravertebral block. Although lumbar sympathectomy failed to give relief in one of these cases (Case 2), a bilateral operation was performed in another case (Case 1) with excellent results. It is our feeling that subjective relief, as shown by an increase in "walking distance," affords a better index of the relief of symptoms to be expected from sympathectomy than does the claudication test. We have used this test, however, to obtain objective evidence of the significance of sympathetic vasoconstrictors in aggravating the symptom of intermittent claudication.

SUMMARY AND CONCLUSIONS

1. By means of a claudication test, objective evidence was obtained in seven cases that there was an increase in the ability of the muscles to work after procaine injection of the lumbar sympathetic ganglia. In three additional cases there was subjective improvement after the injection. Six of the patients who obtained relief from paravertebral procaine injection were subsequently subjected to lumbar sympathectomy, and on two of these a bilateral lumbar sympathectomy was performed. Immediate and persistent relief was obtained in five of the cases. There were no untoward results.

2. An explanation is adduced to harmonize the beneficial results of sympathectomy in our cases with the recognized physiologic effect of sympathetic stimulation, which produces an increase of blood flow through normal human muscle.

3. All except one of the patients who were studied showed evidence of obliteration of major arteries of the legs. In all but one of the cases there was clinical evidence of abnormal vasoconstriction, in addition to the organic vascular occlusion. Although it is true that intermittent

claudication is caused by arterial obstruction which is most frequently organic in character, in certain cases there may be an additional element of abnormal vasoconstriction which aggravates the circulatory deficiency. Lumbar sympathectomy gives promise of benefit in these cases.

CASE REPORTS

CASE 1.—H. T. (Graduate Hospital #122,459), a white man, aged 67 years, was admitted to the clinic with the chief complaint of intermittent claudication in both legs of two years' duration. His walking was limited to one block, and the pain was more severe on the left side. He gave a history of typical attacks of Raynaud's spasm of the digital vessels of both hands for thirty-five years. His feet were constantly cold and blue. He had developed a small lesion at the tip of the left second toe. Varicose veins of both sides had been treated by ligation and injection, without relief. He smoked from eight to ten cigarettes a day. Physical examination showed a frail, elderly man, with a marked arcus senilis. Both femoral pulses were palpable, but no pulsation could be felt in the lower arteries of the legs. Oscillations were present at the right ankle but were barely perceptible on the left side. A vasodilatation test (heat applied to the arms) produced a rise of the skin temperature of the toes on the left side to 27.2° C., whereas, on the right side, the temperature came to only 21.9° after eighty minutes of heat. Roentgenograms of the lower portions of the legs showed calcification of some of the vessels. After paravertebral procaine block of the second, third, and fourth left sympathetic ganglia, the skin temperature rose to 28.5° C., but the claudication test showed no improvement, although the appearance of pain was delayed. He was surprised to find that his walking distance had been increased threefold for a period of one hour after the injection. One week later, 3 c.c. of a 2 per cent procaine solution were injected into the region of the left second, third, and fourth lumbar ganglia, and, when a good rise in skin temperature was obtained, 3 c.c. of 100 per cent alcohol were injected beneath the second and third ganglia. He was relieved of his claudication for three months. At the end of that time the claudication returned on the left side, and accordingly he was subjected to a left-sided lumbar sympathectomy. After recovery from this operation he was completely relieved of his claudication on the left side. Six months later, a right-sided lumbar sympathectomy was performed. At present, 1.5 years after operation, he can walk fifteen blocks without pain, and both feet are warm and of good color. The lesion of the tip of the left second toe has healed. Oscillations at the left ankle are still greatly reduced, but his symptoms have been relieved.

CASE 2.—H. McC. (Hospital of the University of Pennsylvania #45,188), a white man, aged 41 years, was admitted to the clinic with the chief complaint of claudication in the right hip and calf of three years' duration; this was increasing in severity, so that, when he was first seen, he was able to walk only 100 yards before he was stopped by pain. He did not complain of coldness of either foot. He had smoked one and one-half packages of cigarettes daily for fifteen years. Six months before admission he was found to have hypertension, with a systolic pressure over 200 mm. Hg. His father died of cerebral apoplexy at the age of 43. On physical examination there were marked sweating and cyanosis of both feet. On the right side the femoral pulse could be felt, but it was of poor quality. On the left side the dorsalis pedis pulsations could be felt. Roentgenograms showed no evidence of calcification of the vessels of the lower portions of the legs. His blood pressure was 180/110. The electrocardiogram was normal, and the orthodiagram

showed no enlargement of the heart. The eye grounds showed contracted vessels but no hemorrhages or exudate. The urine was normal and showed good concentration, and the phenolsulphonephthalein test showed 60 per cent excretion at the end of one hour and an additional 20 per cent at the end of two hours. The blood sugar was 98 mg. per cent. The blood Wassermann reaction was negative. After paravertebral procaine block of the eleventh and twelfth thoracic and first and second lumbar ganglia on the right side, the skin temperature of the toes rose to 32.5° C. Although the amplitude of contraction of the calf on stimulation was not materially increased, the pain which the patient developed during the first claudication test did not appear after the lumbar sympathetic block. His "walking distance" increased from 100 to 500 yards after the block. A right-sided lumbar sympathectomy was performed, and the first, second, and third lumbar ganglia were removed. Because of the hypertension the major and minor splanchnic nerves were resected at this operation. After operation, the blood pressure fell and became stabilized at 140/70, and his right foot became warm and dry. A pulsation in the medial and lateral geniculate arteries was felt. Sweating was absent on the right side below the groin. After operation his walking distance was still limited by muscular weakness, but the severe pain and numbness in the hip had disappeared.

CASE 3.—T. D. (Hospital of the University of Pennsylvania), a white man, aged 46 years, was admitted to the clinic with the chief complaint of claudication in the left hip and calf of one year's duration and claudication in the right calf of six years' duration.

The patient had noticed a gradual onset of intermittent claudication in the right calf six years previously, so that walking was limited to two blocks. At that time he was examined by Dr. Eugene M. Landis, to whom we are indebted for the following information. The right dorsalis pedis and posterior tibial pulses were not palpable. Those on the left were present. After procaine infiltration of the right posterior tibial nerve, the temperature of the toes increased to 32.3° C. The claudication test showed that there was some arterial occlusion in the right calf, but the left leg was normal. The patient gave a history of mild migraine, with two attacks of transient, left-sided hemiplegia, presumably as a result of cerebral vascular spasm. The diagnosis at this time was arterial occlusion, with marked vasospasm.

During the succeeding six years the claudication on the right side gradually disappeared, but one year prior to admission he developed severe claudication on the left side, involving the left hip and the left calf. His walking was then limited to one-half block. The left foot also became cold, white, and numb when it was exposed to cold. On examination, the dorsalis pedis pulse was present on the right, but the posterior tibial on the right and both ankle pulses on the left were absent, although an aberrant artery, just anterior to the left external maleolus, was palpable. Roentgenologic examination showed calcification of the dorsalis pedis arteries and the posterior tibial arteries in the lower third of the legs. However, there was no calcification of the vessels of the upper part of the leg, iliac vessels, or aorta. A vasodilatation test (heat applied to the arms) gave a normal response on the right side, but on the left side the skin temperature rose to only 28.2° C. The oscillations were better on the left side than on the right. The claudication test gave evidence of impairment on both sides, worse on the left than the right. After procaine injection of the left lower thoracic and upper lumbar sympathetic ganglia (twelfth thoracic and first, second, and third lumbar), there were lessening of the claudication and a marked increase in ability to walk. Instead of being stopped after half a block by pain in the left calf, he was now able to walk four blocks before the pain in the right calf brought him to a halt. The skin temperature after the procaine block rose to 33.1° C. A left-

sided lumbar sympathectomy was performed, and the first, second, and third lumbar ganglia were removed. His pain was relieved entirely on the left side, but he was still troubled by claudication in the right calf. Four weeks later a right-sided lumbar sympathectomy was performed, with removal of the first, second, and third lumbar ganglia. Since the second operation he has been able to walk as far as nine miles without intermittent claudication.

Comment.—This patient had been studied over a period of six years. Abnormal vasoconstriction was present when he was first seen, but the degree of arterial occlusion had varied. It was first more marked on the right, but thereafter had increased on the left side while collateral circulation had developed on the right side. There is a possibility that the arterial occlusion was precipitated by the abnormal vasoconstriction. That vasoconstriction exaggerated the disability was substantiated by the improvement which followed lumbar sympathectomy.

CASE 4.—J. L. (Hospital of the University of Pennsylvania #45,892), a white man, aged 65 years, was admitted to the clinic with the chief complaint of intermittent claudication in both legs of eight months' duration. Eight years earlier he had suffered a left-sided cerebral vascular accident, the exact nature of which was uncertain. On physical examination, no pulses were present on the left side below the femoral, but the posterior tibial pulse could be felt on the right side. Roentgenologic examination showed no evidence of calcification of the vessels of the lower portions of the legs. The blood sugar was 86 mg. per cent, and the Wassermann reaction was negative. Oscillometric examination at the ankles showed no oscillations on the left side and only ¼ point on the right. The feet blanched on elevation, the left in fifteen seconds and the right in forty seconds; when they were brought back to the horizontal position there was delayed return of color, especially on the left side. The blood pressure was 102/70. Both feet were cold and moist, with an irregularly mottled appearance of the skin of the lower parts of the legs. The skin of the left toes was slightly edematous and shiny, and there was rubor on the left side. During a vasodilatation test the skin temperature rose to 29.2° C. on the right, whereas, on the left side, it rose to only 21° C. The patient received suction and pressure treatment of both legs for one month, without relief. A left paravertebral procaine block was performed by inserting three needles in the eleventh thoracic and first and second lumbar ganglia. The skin temperature of the left toes rose to 32.2° C. Although the claudication test showed no improvement, as a result of the injection he was able to walk three times as far without developing pain in the left calf.

Comment.—This patient, who showed marked evidence of organic vascular occlusion, also had an element of abnormal vasoconstriction. If he fails to improve with conservative treatment, lumbar sympathectomy will be advised.

CASE 5.—J. C. (Hospital of the University of Pennsylvania #41,114), a white man, aged 33 years, was admitted to the clinic with the chief complaint of intermittent claudication in the right calf after walking one block, and migratory phlebitis of three years' duration. In addition, the right foot was cold, blue, and painful. He had been treated with a 3 per cent saline solution and typhoid vaccine intravenously. A right-sided lumbar sympathectomy by the transperitoneal route had been attempted in another hospital, but the sympathetic ganglia had not been found because of dense adhesions. No relief from his vasoconstriction was obtained, although the lesion on the right foot subsequently healed. There were marked varicose veins of the right leg. Roentgenologic examination showed no evidence of calcification of the arteries of either leg. On the right side no pulses were palpable below the femoral, but on the left side both the dorsalis pedis and the posterior tibial pulses were present. There was marked blanching

of the right leg on elevation, with delayed return of color in the right foot, but the right foot was warmer than the left.

Oscillations on the right side were absent even above the knee, and there was only ¼ unit on the left side at the ankle. There were increased sweating and cyanosis when he was exposed to the emotional stimulation of examination. A vasodilatation test showed that there was an adequate circulation on the left side, but a definitely impaired circulation on the right side; the skin temperature rose to only 26.4° C. on the right middle toe. Biopsy of a thrombosed vein of the leg substantiated the diagnosis of thromboangiitis obliterans. The claudication test showed slight impairment of the function of the left calf and marked impairment on the right side. After injection of the right twelfth thoracic and first, second, and third lumbar ganglia, the skin temperature rose to 29.1° C., and objective improvement occurred, as shown by the claudication test, although there was only a slight increase in his "walking distance."

The varicose veins of the right leg were eliminated by high ligation of the long saphenous vein. Some badly diseased tonsils were removed, and the patient was told to stop smoking entirely. Under this treatment his walking distance increased to two blocks, and the circulation in the right foot became fairly adequate.

Comment.—This patient improved on conservative treatment, which consisted of eradication of focal infection, cessation of smoking, proper care of the feet, and elimination of the varicose veins. It is our belief that sympathectomy would offer him only partial relief from his intermittent claudication, for the subjective relief after paravertebral block was only slight. Operation has been postponed for the present.

CASE 6.—F. D. (Hospital of the University of Pennsylvania #26,115), a white woman, aged 52 years, was admitted to the clinic with the chief complaint of cold feet and intermittent claudication, especially in the right calf, with pain after walking one-half block.

On examination, no pulses were palpable below the femoral on either side. She was given tissue extract injections and a long course of suction and pressure treatment without much relief. Her varicose veins disappeared after a high and mid-thigh ligation of the long saphenous veins. In spite of the elimination of her varicosities, the claudication was not lessened. A vasodilatation test showed impairment of the circulation on both sides; on the right side the temperature of the middle toe rose to only 27.3° C., and, on the left side, to 25.4° C. She received massive doses of vitamin B_1 intravenously, without improvement.

Paravertebral procaine block at the first, second, and third lumbar ganglia produced a good rise in the temperature of the toes. However, there was no increase in her walking distance. She still has intermittent claudication, after half a block, in the calves and feet on both sides.

Comment.—This patient presented evidence of widespread organic arterial occlusion, without clinical evidence of abnormal vasoconstriction. The fact that she was not relieved of her claudication by paravertebral procaine block, even though there was a good rise in the skin temperature of her toes, suggested that she would not be relieved by lumbar sympathectomy. Operation was not recommended.

CASE 7.—L. P. (Hospital of the University of Pennsylvania #44,330), a white woman, aged 40 years, was admitted to the clinic with a diagnosis of diabetes and a complaint of poor eyesight and numbness and tingling of the extremities. This patient's diabetes was discovered at the age of 13, and she had been under treatment with insulin and dietary regulation since 1922. About three years before admission she developed numbness and tingling in her extremities. Her feet were usually cold and became red on exposure to cold air or cold water. The numbness and tingling were not related to cold. On examination, vibratory sensation was

absent in both feet below the ankles and was decreased in the lower portions of the legs. Touch and pain sensations were also diminished. The reflexes were active. There was clinical evidence of abnormal vasoconstriction, with cold, moist, blue extremities. There was considerable intermittent claudication, so that she was stopped at the end of two blocks by pain in both calves. Both posterior tibial pulses were present, but the dorsalis pedis pulses could not be felt. Paravertebral procaine block on the right side produced a rise in skin temperature to 31.6° C., but no improvement was demonstrable by the claudication test. Her walking distance was not increased.

Comment.—In spite of the fact that this patient gave evidence of abnormal vasoconstriction, her chief complaint was not coldness of her feet, but numbness, tingling, and claudication. Because there was no response to paravertebral procaine block, lumbar sympathectomy was not advised.

CASE 8.—A. S. (Graduate Hospital #146,729), a white man, aged 37 years, was admitted to the clinic with the chief complaint of intermittent claudication in both calves of three years' duration, and a painful ulcer of the right great toe of one year's duration. He had received hot baths for this condition, without improvement. Examination showed extensive obliteration of the arteries. No pulses could be felt in either leg below the femorals. There was rubor of the right foot. A tender "crack" at the tip of the right great toe had shown no tendency to heal in six months. His walking was stopped after one block by intermittent claudication in the calves. He smoked a package of cigarettes daily.

The oscillometric reading at the right ankle was 3.5, and, at the left, only 1.5. A vasodilatation test (heat applied to the arms) showed that there was a good collateral circulation on the left, but only a fair one on the right. The claudication test showed marked impairment in the circulation to the left calf, but the blood vessels of the right side were less severely damaged. After paravertebral procaine block of the right twelfth thoracic and second and third lumbar ganglia, there was an increase in the temperature of the toes to 30.1° C., and the amplitude of contractions was slightly increased. However, he was now able to walk four blocks before he noticed pain in the right calf. He stopped smoking, but without relief of his pain. A right-sided lumbar sympathectomy was then performed. The first, second, and third lumbar ganglia were removed. After operation his walking distance was increased to eight blocks, and the lesion on the great toe healed.

Comment.—Even though the arterial occlusion was more marked in the proximal part of the left leg, the right foot was in more imminent danger because an open lesion due to vascular insufficiency was present. Sympathectomy was therefore performed first on this side. There was evidence of abnormal vasoconstriction on the left side, in addition to the arterial occlusion. If he does not improve, a left-sided lumbar sympathectomy will be advised.

CASE 9.—A. N. (Graduate Hospital #144,398), a white man, aged 32 years, was admitted to the clinic with the chief complaint of intermittent claudication in the right calf of one month's duration. The patient had had a sudden onset of pain in the right calf, with numbness and coldness of the right foot. His walking was restricted to a half block. Treatment by contrast bathing, tissue extract, and an arch support failed to give relief. On examination, the right femoral artery was found to be occluded above the popliteal. The left dorsalis pedis pulse was absent, although the left posterior tibial was normally palpable. The right ulnar pulse was absent. When he was first seen, he was smoking one and a half packages of cigarettes daily. Under instruction he stopped smoking, but his walking was still limited to one block. There was marked rubor of the right foot, with immediate blanching on elevation and delayed filling of the veins with dependency (thirty seconds). There was no evidence of acute migratory phlebitis, although

pigmentation as a result of previously inflamed veins was apparent on both legs. In addition, there was evidence of marked, abnormal vasoconstriction, as shown by cyanosis and increased sweating of both feet. Injection of procaine into the region of the right first, second, third, and fourth lumbar sympathetic ganglia brought about a prompt increase in the skin temperature to 30.5° C. A claudication test before the block showed marked limitations of muscle power. After paralysis of the sympathetic vasoconstrictor fibers, the amplitude of contraction was greatly increased, and he was able to walk three blocks without pain. The first and second right lumbar sympathetic ganglia were resected. He recovered from the operation without complications. His walking distance was immediately increased to eight blocks, and the right foot has remained warm and pink. He has been almost entirely relieved of his symptoms. Even though there is evidence of abnormal vasoconstriction on the left side, with loss of one of the ankle pulses, he has no symptoms in this leg, and, therefore, bilateral lumbar sympathectomy has not been recommended.

CASE 10.—L. T. (Hospital of the University of Pennsylvania #46,515), a white man, aged 42 years, was admitted to the clinic with the chief complaint of claudication in the left foot and calf of three years' duration. At first he could walk seven blocks, but recently had been limited to three blocks. The left foot was cold and numb. He had paresthesias over the left great toe. He smoked one package of cigarettes daily. Treatment had consisted of intravenous injections of citrate solution, from which he had obtained no relief. On examination, there was rubor on dependency, with blanching on the left in thirty seconds, and, on the right, in one minute. Rubor returned in eight seconds on the left side and in five seconds on the right. On the right side the posterior tibial pulse could be felt, but on the left side neither ankle pulse was palpable. The blood pressure was 122/96. Oscillometric readings at the right ankle were 4 units, and at the left, 0. A vasodilatation test (heat applied to the arms) showed that he was able to develop a normal blood flow on the right side; the temperature of the toes rose to 32.5° C. On the left side the temperature rose to 27.6° C. After injection into the left lumbar sympathetic ganglia, the skin temperature rose to 30.8° C., and the claudication test showed that a considerable increase in the amount of work could be performed. However, on walking, he was still stopped by the pain after three blocks. Although he presented evidence of abnormal vasoconstriction, it was felt that sympathectomy would not relieve him of his intermittent claudication, and, therefore, it was not advised.

CASE 11.—C. K. (Hospital of the University of Pennsylvania), a white man, aged 59 years, was admitted to the clinic with the chief complaint of intermittent claudication in the left calf, foot, and thigh of five years' duration. The patient noticed a gradually increasing weakness and discomfort in the left calf on walking uphill. There was no history of migratory phlebitis, nor did he complain of coldness in either foot. On examination, he was found to have a blood pressure of 150/80. The pulses were normal in the upper extremities. The right dorsalis pedis pulse was not palpable, and no pulsation could be felt on the left side below the femoral. There was abnormal blanching of the left foot on elevation, but filling on both sides returned within eighteen seconds. The oscillometric readings at the ankles on both sides were approximately normal. The claudication test showed abnormal fatigue, with pain, on the left side, and some fatigue, without pain, on the right side. The vasodilatation test (heat applied to the arms) showed a normal response on the right side, but on the left side there was no increase of the temperature of the toes. Roentgenograms showed no calcification of the vessels. Injection of procaine into the region of the left eleventh and twelfth thoracic and first and second lumbar sympathetic ganglia resulted in a good rise of skin

temperature, with disappearance of sweating and dilatation of the veins of the lower leg. Considerable improvement was demonstrated by the claudication test, and his walking distance was definitely increased, so that, instead of being stopped by pain after climbing two flights of stairs, he was able to climb four flights without discomfort. Lumbar sympathectomy was advised, but the patient decided to try conservative treatment.

CASE 12.—A. M. (Hospital of the University of Pennsylvania #41-48,766), a white man, aged 60 years, was admitted to the clinic with the chief complaint of intermittent claudication in both calves and the right thigh of three months' duration. The onset of symptoms had been gradual, and, when he was seen, his walking was limited to two blocks. He had received no treatment for this condition. He smoked approximately ten pipefuls of tobacco per day. On examination, all ankle pulses were present, but the feet were cold and blue, although they were not moist. The veins were markedly contracted (Fig. 1). The oscillations at the ankles were normal on the left side and only slightly reduced on the right side. The blood pressure was 128/70. Roentgenograms of the legs showed no calcification of the vessels of the lower portion of the leg and foot.

The blood urea nitrogen was 11 mg. per cent, and the phenolsulphonephthalein excretion, 77 per cent. The heart was moderately enlarged (+21 per cent in the orthodiagram), and there were slurring of the QRS complex in the electrocardiogram and benign sclerosis of the retinal vessels.

After the injection of procaine into the region of the right first, second, and third lumbar ganglia, the skin temperature of the toes rose to 32.2° C., and the oscillation at the ankle increased from 3 to 9 units. His walking distance was increased from two to eight blocks immediately after the injection, and the claudication test showed a considerable increase in the amplitude of contraction. The first, second, and third lumbar ganglia on the right were resected, and, after the operation, he was completely relieved of his intermittent claudication on this side.

REFERENCES

1. Lewis, T., Pickering, G. W., and Rothschild, P.: Observations Upon Muscular Pain in Intermittent Claudication, Heart **15:** 359, 1931.
2. Veal, J. R., and McFetridge, E. M.: Vascular Changes in Intermittent Claudication With a Note on the Value of Arteriography in This Symptom Complex, Am. J. M. Sc. **192:** 113, 1936.
3. Homans, J.: Circulatory Diseases of the Extremities, New York, 1939, The Macmillan Co.
4. Landis, E. M., and Montgomery, H.: In Barr, D. P.: Modern Medical Therapy in General Practise, Baltimore, 1940, Williams & Wilkins Co., vol. 3.
5. Brown, G. E.: The Treatment of Peripheral Vascular Disturbances of the Extremities, J. A. M. A. **87:** 379, 1926.
6. Flothow, P. G.: Diagnostic and Therapeutic Injections of the Sympathetic Nerves, Am. J. Surg. **14:** 591, 1931.
7. Morton, J. J., and Scott, W. J. M.: The Quantitative Determination of Vasoconstriction Spasm as a Basis for Therapy in Peripheral Arterial Diseases, Ann. Surg. **96:** 754, 1932.
8. Reichert, F. L.: Intermittent Claudication Without Gangrene Controlled by Sympathetic Nerve Block, Ann. Surg. **97:** 503, 1933.
9. Telford, E. D.: Sympathectomy; Review of 100 Operations, Lancet **1:** 444, 1934.
10. Harris, R. I.: The Role of Sympathectomy in the Treatment of Peripheral Vascular Disease, Brit. J. Surg. **23:** 414, 1935.
11. White, J. C.: Progress in Surgery of the Autonomic Nervous System in 1935, New England J. Med. **215:** 453, 1936.
12. Davis, J.: Intermittent Claudication, Lumbar Sympathectomy, Časap. lék. česk **75:** 1677, 1936.
13. Pearl, Fleix, L.: Angiospastic Claudication With a Report of 6 Cases, Am. J. M. Sc. **194:** 505, 1937.

14. Grant, R. T., and Pearson, R. S. B.: The Blood Circulation in the Human Limb; Observations on the Differences Between the Proximal and Distal Parts and Remarks on the Regulation of Body Temperature, Clin. Sc. **3**: 119, 1938.
15. Holling, H. E.: Observations on the Oxygen Content of Venous Blood From the Arm Vein and on the Oxygen Consumption of Resting Human Muscle, Clin. Sc. **4**: 103, 1939.
16. Kunkel, P., Stead, E. A., Jr., and Weiss, S.: Blood Flow and Vasomotor Reactions in the Hand, Forearm, Foot, and Calf in Response to Physical and Chemical Stimuli, J. Clin. Investigation **18**: 225, 1939.
17. Abramson, D. I., and Ferris, E. B., Jr.: Responses of Blood Vessels in the Resting Hand and Forearm to Various Stimuli, Am. Heart J. **19**: 541, 1940.
18. Hitzrot, L. H., Naide, M., and Landis, E. M.: Intermittent Claudication Studied by a Graphic Method, Am. Heart J. **11**: 513, 1936.
19. White, J. C.: Diagnostic Blocking of Sympathetic Nerves to Extremities With Procaine. A Test to Evaluate the Benefit of Sympathetic Ganglionectomy, J. A. M. A. **94**: 1382, 1930.
20. Batson, O. V.: The Function of the Vertebral Veins and Their Role in the Spread of Metastases, Ann. Surg. **112**: 138, 1940.
21. Royle, N. D.: The Treatment of Spastic Paralysis by Sympathetic Ramisection, Surg., Gynec. & Obst. **39**: 701, 1924.
22. Flothow, P. G.: Anterior Extraperitoneal Approach to the Lumbar Sympathetic Nerves, Am. J. Surg. **29**: 23, 1935.
23. Pearl, F. L.: Muscle-Splitting Extraperitoneal Lumbar Ganglionectomy, Surg. Gynec. & Obst. **65**: 107, 1937.
24. Hoskins, R. G., Gunning, R. E. L., and Berry, R. L.: The Effects of Adrenin on the Distribution of the Blood, Am. J. Physiol. **41**: 513, 1916.
25. Leriche, R.: The Surgery of Pain, Translated and Edited by Archibald Young, Baillière, Tindall & Cox, London, 1939, p. 40.
26. Roome, N. W.: The Effects of Intra-Arterial Epinephrin on the Blood Flow in an Extremity, Am. J. Physiol. **123**: 543, 1938.

DISCUSSION

Dr. Kenneth W. Thompson, New Haven, Conn.—There is one other aspect of this problem to which, I believe, we should pay attention, namely, the possible hormonal relationship between muscle metabolism and blood flow. I have in mind a patient, a eunuchoid, who began treatment with testosterone at the age of about 29, after which there was no question in anyone's mind that his leg muscles hypertrophied. You may also recall the fact that in the female guinea pig the masseter muscles hypertrophy while the animals are being treated with testosterone. We are also familiar with the atrophied muscles of elderly men.

There seems to be no question now that the giving of testosterone changes the nitrogen balance of the body, causes a storage of nitrogen, and greatly alters muscle metabolism. Dr. Albright, of Boston, has given us some astounding data on this subject. It may be that this sort of hormonal relationship has something to do with whether or not sympathectomy produces the desired results. Suppose an elderly man who had been deficient in one of those postulated hormones for ten or fifteen years develops complaints referable to muscle pain, and sympathectomy is done. It probably does not alter his muscle metabolism very much. When the patient is younger, with a complaint caused by occlusion, perhaps from Buerger's disease or trauma, sympathectomy may very well result in a great deal more benefit, purely from the effect of the sympathectomy on blood flow.

This hormonal balance may have a bearing on some of the other phases of the problem, such as the collateral circulation of the heart. I believe we must not neglect this phase of the subject in discussing sympathectomy.

Dr. Norman E. Freeman, Philadelphia.—The question whether parasympathetic nerves supply blood vessels of muscles and produce vasodilatation has not been answered. Years ago I was interested in this problem from the standpoint of

blood pressure reactions in sympathectomized animals and did find evidence that there was some system outside the sympathetic nervous system which could cause changes in blood pressure. I am not sure what part such nerves might play in the production of vasodilatation in muscles after removal of the sympathetic fibers.

The clinical observation that anterior root section will produce much the same circulatory pattern in the lower extremities as that obtained from sympathectomy, however, would suggest at least that efferent fibers traverse the anterior roots.

As far as Dr. Thompson's comments are concerned, I believe his observations on the effect of testosterone on intermittent claudication are very interesting. The patients on whom we have operated were not only patients with Buerger's disease, but patients with arteriosclerosis, as well. Lumbar sympathectomy, although it apparently will cause sterility, does not necessarily affect potency. One of the patients who was operated upon was 71 years old. He had no pulse in his left leg, but he had evidence of severe arterial vasoconstriction. He gave a history of Raynaud's disease in his hands for thirty-five years, and the feet were typically cold, blue, and moist, with contracted veins. The response in his case makes one feel at least that there is some vasoconstrictor activity which is interfering with the normal supply of blood to the working muscles.

CEDILANID, WITH SPECIAL REFERENCE TO ITS INTRAVENOUS USE

MAURICE SOKOLOW, M.D., AND FRANCIS L. CHAMBERLAIN, M.D.
SAN FRANCISCO, CALIF.

THE use of the ordinary whole leaf of digitalis, the digitalis purpurea of the United States Pharmacopeia, has never been considered ideal for several reasons. First, it required bio-assay; second, it was impure and hence could not be given intravenously with assurance; third, its potency has varied from time to time, as shown by the fact that the U.S.P. XI digitalis is one-third stronger than that of the U.S.P. X. In recent years the glycosides of digitalis have been isolated in pure crystalline form, and work is being done with these pure substances. In addition to the ordinary digitalis, digitalis purpurea, there is another plant, digitalis lanata, which is indigenous to the Balkan countries. Stoll[1] has isolated the glycosides of this new digitalis. There are three glycosides in each, but digitalis lanata differs in that it alone contains lanatoside C, or cedilanid. Clinical interest in lanatoside C began with the pharmacologic work of Moe and Visscher[2] on heart-lung preparations. This suggested that lanatoside C was the least toxic and the most potent of the lanata glycosides and could be obtained in pure crystalline form.

Early preliminary work in Europe[3] (the drug was first available in Switzerland) indicated that lanatoside C was a potent drug. It has been used in the United States for the past two years. Gold and his coworkers,[4] in New York, and Fahr and LaDue,[5] in Minneapolis, have made preliminary reports. During the past two years we have been studying the oral and intravenous use of lanatoside C at the University of California Hospital, and our reports are based on that work.[6] To date we have followed eighty-five patients. The drug* comes in tablets of 0.5 mg., as well as in 2 c.c. and 4 c.c. ampoules which contain 0.2 mg. per cubic centimeter. It has been established that the cat unit is equal to 0.28 mg.; however, Gold showed that 1 mg. of cedilanid is equal to 293 mg. of digitalis leaf when they are compared by the cat method, to 438 mg. when they are compared by the frog method, and to 170 mg. when they are compared in man by oral administration. Therefore, the clinical potency of these pure glycosides should be ascertained by clinical assay and not by animal assay.

The intravenous administration of cedilanid has proved to be of great value. We have used it in thirty-eight cases in doses up to 14 c.c. per

From the Department of Medicine, University of California Medical School, San Francisco.

Presented before the meeting of the California Heart Association, Del Monte, Calif., May 4, 1941.

Received for publication Sept. 2, 1941.

*Marketed by the Sandoz Chemical Works, Incorporated, to whom we are grateful for supplies.

day, some of which were divided. In general, 8 c.c. per day is the digitalizing dose, and 6 c.c. to 14 c.c. in twenty-four hours in divided doses will digitalize almost all patients. In only three instances was mild nausea produced by 8 c.c. of cedilanid given in one dose, and in many instances beneficial effects were noted in ten to twenty minutes. In auricular fibrillation the ventricular rate may fall 40 to 50 beats within thirty minutes to two hours; in auricular flutter a fixed 4 to 1 block, and, subsequently, normal rhythm may be produced by a single dose of 8 c.c. administered intravenously. In cases of normal rhythm with congestive failure, digitalization may be accomplished within twenty-four hours. The advantages of rapid, safe digitalization are self evident in cases of desperate cardiac failure. Frequently, partial digitalization may be accomplished by the intravenous administration of 4 c.c. to 6 c.c., and then maintained by the oral preparation. The intravenous preparation is not recommended for maintenance because frequent injections are necessitated by the rapid excretion of the drug. It is, therefore, better to use the oral preparation of cedilanid for maintenance. In general, we find that a daily maintenance dose of 1 c.c. to 3 c.c. is needed when the drug is given intravenously.

CONCLUSIONS

1. Cedilanid is a pure, crystalline glycoside which is obtained from digitalis lanata and is not present in digitalis purpurea.

2. Cedilanid is marketed in tablets of 0.5 mg. for oral use, and in ampoules in which each cubic centimeter is equal to 0.2 mg.

3. The intravenous digitalizing dose varies from 8 c.c. to 14 c.c. in twenty-four hours.

4. Rapidity of action is the most striking clinical feature of cedilanid.

REFERENCES

1. Stoll, Arthur: The Cardiac Glycosides, London, 1937, Pharmaceutical Press.
2. Moe, G. K., and Visscher, M. B.: Studies on the Native Glucosides of Digitalis Lanata, J. Pharmacol. & Exper. Therap. **64:** 65, 1938.
3. (a) Junet, R., and Bianchi, M.: Etude clinique d'un nouveau digitalique: le digilanide, Rev. méd. de la Suisse Rom. **59:** 139, 1939.
   (b) Michaud, L.: L'emptoi du digilanide C en clinique, Schweiz. med. Wchnschr. **19:** 1338, 1938.
   (c) Wayne, E. J.: Clinical Observations on Two Pure Glucosides of Digitalis, Digoxin and Digitalinum Verum, Clin. Sc. **1:** 63, 1933.
4. (a) Gold, Harry: Digitalis in Heart Failure, N. Y. State J. Med. **41:** 496, 1941.
   (b) Gold, Harry, Kwit, N. T., and Cattell, McKeen: Studies on Purified Digitalis Glucosides. I., J. Pharmacol. & Exper. Therap. **69:** 177, 1940.
   (c) Kwit, N. T., Gold, H., and Cattell, McKeen: Studies on Purified Digitalis Glucosides. II., J. Pharmacol. & Exper. Therap. **70:** 254, 1940.
   (d) Cattell, McKeen, and Gold, Harry: Studies on Purified Digitalis Glucosides. III., J. Pharmacol. & Exper. Therap. **71:** 114, 1941.
5. Fahr, George, and LaDue, John: A Preliminary Investigation of the Therapeutic Value of Lanatoside C (Cedilanid), AM. HEART J. **21:** 133, 1941.
6. Chamberlain, Francis L., and Sokolow, Maurice: Clinical Experience With the Oral Administration of Cedilanid, and a Comparison of the Oral and Intravenous Preparations of Cedilanid With Digitalis Purpurea, AM. HEART J. **23:** 245, 1942.

CLINICAL EXPERIENCE WITH THE ORAL ADMINISTRATION OF CEDILANID, AND A COMPARISON OF THE ORAL AND INTRAVENOUS PREPARATIONS OF CEDILANID WITH DIGITALIS PURPUREA

FRANCIS L. CHAMBERLAIN, M.D., AND MAURICE SOKOLOW, M.D.
SAN FRANCISCO, CALIF.

IN OUR first paper[1] the history and pharmacology of cedilanid and the use of the intravenous preparation were discussed. In this paper we shall summarize our experience with the oral administration of cedilanid and compare the oral and intravenous preparations with digitalis purpurea.

The digitalizing dose was ascertained in forty-five cases. Nine patients were digitalized in twenty-four hours with a dose varying from 4 to 7 mg.; six patients, in forty-eight hours with 5 to 15 mg.; fifteen patients, in seventy-two hours with 5.3 to 9.3 mg.; five patients, in ninety-six hours with 6 to 16 mg.; and three patients, in 120 hours with 9 to 10 mg. The maintenance dose was ascertained in forty-seven cases. It varied from 0.5 to 2.5 mg.; the average was 1.6 mg. (3 tablets) daily. Assuming an average maintenance dose of 1.6 mg., and calculating all doses for a period of seventy-two hours, we obtained an average digitalizing dose of 7.5 mg.

Therefore, we conclude that a satisfactory method for the administration of cedilanid would be to give 6 to 7.5 mg. in about seventy-two hours. If the tablets of 0.5 mg. which are now on the market are used, a total of 12 to 15 tablets would be required. Eight tablets, or 4.0 mg., may be given on the first day in divided doses, and 4 tablets daily thereafter. When therapeutic effects are evident, or if initial toxic manifestations appear, the dosage should be decreased.

Since the acceptance of Withering's work, many substitutes, with elaborate claims of advantage over digitalis purpurea, have appeared on the market, but none has proved superior and nearly all are much more expensive. An exact comparison between the action of cedilanid and that of digitalis purpurea on human beings is difficult because patients do not have consecutive, identical attacks of congestive failure. In twenty-one cases in which the manifestations were reasonably parallel, the average maintenance dose of cedilanid was 1.6 mg., and, of digitalis

From the Department of Medicine, University of California Medical School, San Francisco.

Presented before the meeting of the California Heart Association, Del Monte, Calif., May 4, 1941.

Received for publication Sept. 2, 1941.

purpurea, 0.13 Gm. This is 5.7 cat units of cedilanid to 1.3 cat units of digitalis purpurea. The toxic manifestations were similar. Of ninty-five patients who were treated with cedilanid, approximately one-third showed toxicity. This percentage was necessarily high because of experimentation with the dosage. The toxic manifestations disappeared in one to three days, which was about the same period of time as when patients were treated with digitalis purpurea. Prolonged A-V conduction developed in five cases; A-V nodal tachycardia, in one; and auricular fibrillation, in one. The arrhythmias in the last two cases reverted to normal spontaneously in forty-eight to seventy-two hours. The electrocardiographic changes were similar; the T waves, S-T segments, and P-R intervals were affected.

The therapeutic effects of cedilanid and digitalis purpurea were similar, with one important exception. The intravenous preparation of cedilanid acts more rapidly, as was pointed out in our previous paper.[1] Standardization of cedilanid by the gravimetric method appears to be advantageous because it insures constant potency, the lack of which is a recognized disadvantage of digitalis purpurea.[2]

CONCLUSIONS

1. Cedilanid is effective orally in all conditions which are commonly treated with digitalis purpurea.

2. The oral digitalizing dose averages 7.5 mg. in seventy-two hours.

3. The average oral maintenance dose is 1.6 mg.

4. The rapid absorption, constant potency, and rapid action of cedilanid give it advantages over digitalis purpurea.

REFERENCES

1. Sokolow, Maurice, and Chamberlain, Francis L.: Cedilanid, With Special Reference to Its Intravenous Use, AM. HEART J. 23: 243, 1942.
2. Levy, Robert L., Bruenn, Howard G., and Ellis, Samuel S.: Variations in Potency of Certain Commercial Preparations of Digitalis, AM. HEART J. 8: 226, 1932.

ACUTE PERICARDITIS SIMULATING ACUTE CORONARY OCCLUSION

A Report of Fourteen Cases

Arlie R. Barnes, M.D., and Howard B. Burchell, M.D.
Rochester, Minn.

WITHIN recent years we have come to the conclusion that there is, in adults, a distinctive form of acute pericarditis of benign, nonsuppurative nature. In a considerable percentage of these patients, pain in the chest is the most outstanding complaint. Thus, there are occasional patients with precordial pain regarding whom the crucial question arises whether the diagnosis should be acute coronary occlusion or acute pericarditis. The problem is complicated still further by the well-known fact that patients who have acute coronary occlusion may have pericarditis as a complication. The importance of making the correct diagnosis is obvious.

We are reporting fourteen cases in which the differential diagnosis of acute coronary occlusion and acute pericarditis was of paramount importance. In nine of these cases we feel that it can be stated unequivocally that the condition was acute pericarditis; in two cases, that coronary occlusion could be ruled out and that the evidence for acute pericarditis seemed acceptable; and in three cases that acute pericarditis had occurred, but that an associated coronary occlusion had not been excluded definitely, although, in our clinical judgment, it was unlikely. In most of these cases the attending physician was justly in a quandary as to the correct diagnosis. In a few cases in which the attending physician heard a pericardial friction rub, he considered that the proper diagnosis was pericarditis, until doubt was raised in his mind by the electrocardiographic changes which developed. We believe that the type of illness associated with acute pericarditis in adults, accompanied by pain, is crystallized sufficiently in its clinical and electrocardiographic manifestations to justify a detailed report of the cases.

REPORT OF CASES

The study included nine cases of pain in the chest simulating coronary disease, in which the diagnosis of acute pericarditis is considered as established.

Case 1.—The patient was a man, aged 44 years, with no history of previous illnesses. He caught a head cold and possibly had a slight fever on June 3, 1939.

From the Division of Medicine, Mayo Clinic, Rochester.
Read at the Seventeenth Meeting of the American Heart Association, Cleveland, Ohio, May 30, 1941.
Received for publication Sept. 19, 1941.

A week later he developed an intermittent, dull, substernal pain which lasted fifteen to twenty minutes at a time and was not aggravated by effort or relieved by acetylsalicylic acid and codeine. Examination by his physician was negative. By June 24, a progressive, general malaise had developed, and the patient's temperature was found to be 101° F. The following day he was admitted to the hospital, where a pericardial friction rub was found; his temperature was 102.2° F., and his pulse rate, 120. He was given 90 grains (6 Gm.) of sulfanilamide in a period of twenty-eight hours, after which his temperature became normal and remained so. After being in the hospital three weeks, he was dismissed feeling well. He returned to a full, active life without dyspnea or effort distress of any kind and has remained well.

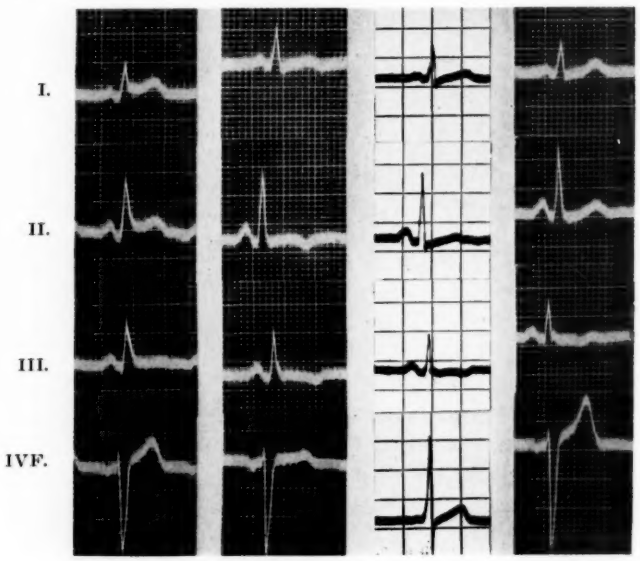

Fig. 1.—Sequence of electrocardiographic changes in Case 1.

The electrocardiograms taken during the patient's illness and after his recovery are reproduced in Fig. 1. The elevation of the S-T segment, particularly in Leads I and II, with the convexity downward, followed, in subsequent electrocardiograms, by negativity of T_2 and T_3, and, finally, by a return to normal, is characteristic of pericarditis and does not fit into any observed sequence of tracings in coronary occlusion.

CASE 2.—A physician, aged 35 years, gave the history that nine years previously, three weeks after tonsillectomy, he had been in bed for one week because of a low substernal pain which never had been explained. It was said that he had no fever and that the roentgenogram of his chest and the electrocardiogram were normal.

The patient's present illness began Dec. 28, 1939, with a common cold which kept him away from his office for two days. A week later (Jan. 3, 1940) he was admitted to the hospital because of a mild pain in his chest of eighteen hours' duration. With the onset of the pain there was a recurrence of soreness of his throat. On admission the patient's temperature, the roentgenogram of his chest, and the electrocardiogram were normal, and the leucocytes numbered 18,000 in each cubic millimeter of blood. On the following day his temperature reached

99.4° F., and the pain in his chest was accentuated by turning to either side in bed, or by swallowing, particularly with the head extended. On the third day in the hospital (January 5) morphine was required for relief of the pain, and a pericardial friction rub was heard for the first time. The low-grade fever and friction rub persisted for five days. The pain gradually disappeared within three weeks. The patient returned to work April 15, 1940, feeling well. One year later (April, 1941) he informed us that he had no further symptoms of any kind.

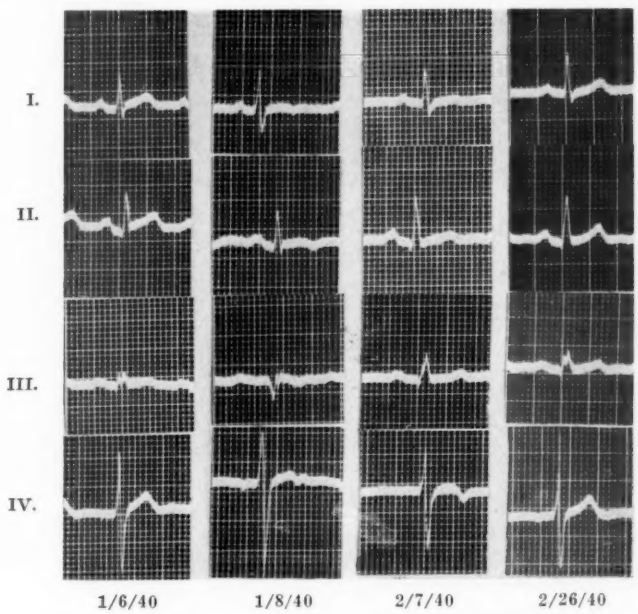

Fig. 2.—Sequence of electrocardiographic changes in Case 2.

The series of electrocardiograms (Fig. 2) shows what we consider a typical picture of pericarditis in all of its stages. The early elevation of the S-T segment in all of the standard leads, and some decrease in the amplitude of the QRS complexes, followed, in subsequent tracings, by inversion of the T wave in all leads, including the chest lead, with return to normal, are practically diagnostic. At no time did a Q or T pattern of coronary occlusion develop.

CASE 3.—The patient was a man, aged 26 years. In the first week of June, 1940, a sore throat and infection of the upper part of the respiratory tract, associated with considerable malaise, developed. On June 21 the patient complained of dull pain under the upper end of the sternum and a sense of retrosternal oppression. On the following day he had an attack of sudden dyspnea of very short duration and was admitted to the hospital. At this time there were slight fever, moderate leucocytosis, and considerable elevation of the sedimentation rate. The only physical sign of note was an accentuated, diastolic, third heart sound. The temperature and leucocyte count were normal twenty-four hours later.

On June 27 the patient was dismissed from the hospital without symptoms, and he returned to work in October. Throughout November and December he continued to work but complained of an occasional precordial burning sensation and of localized precordial pain. However, by April, 1941, he was considered in normal health. The electrocardiograms (Fig. 3) showed changes which, on rapid analysis,

readily could be believed to indicate coronary occlusion, because elevation of the S-T segment in Lead I was accompanied by reciprocal S-T depression in Lead III in the first tracing. Against such a deduction are the absence of a Q pattern in any of the electrocardiograms, the absence of changes in the precordial lead indicating coronary occlusion, the development of negativity of the T wave in all standard leads, and, finally, the relative normality of the tracing at the end of three months.

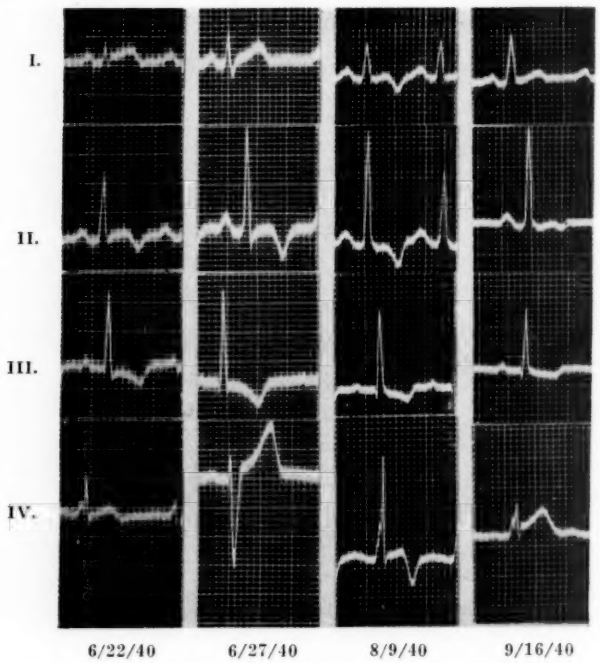

Fig. 3.—Sequence of electrocardiographic changes in Case 3.

CASE 4.—The patient was a farmer's wife, aged 47 years, who previously had been well except for some fatigue of a few months' duration. On Aug. 5, 1940, chilly sensations developed, followed by retrosternal pain extending to the back and slightly to the neck. This pain was aggravated by deep breathing and kept her awake that night. On the following morning she visited a physician who afforded her immediate relief by applying mustard plasters. Early in the morning of August 8, intermittent tachycardia developed, and the patient had a slight nonproductive cough and perspired freely. She registered at the Mayo Clinic on this day. On examination, a loud pericardial friction rub was heard, and her temperature was 101° F. A low-grade fever, friction rub, and intermittent attacks of auricular fibrillation persisted for ten days. The sedimentation rate was elevated to as high as 66 mm. in one hour, but there was no leucocytosis. The patient was comfortable and without complaints within a few days and had no pain after the first day. After three weeks in the hospital she was dismissed feeling well, and her general physical examination gave negative results. In April, 1941, she was feeling well and was active in her work. At this time also, physical examination was negative.

The series of electrocardiographic tracings (Fig. 4) shows a sequence of changes which are characteristic of acute pericarditis. There was, in the early stages, a

slight elevation of the S-T segment, with a concave upper edge, in Leads I and II, followed by the development of negativity of the T wave in all leads. In the second tracings auricular fibrillation was present. In the last tracing the electrocardiogram had returned to normal.

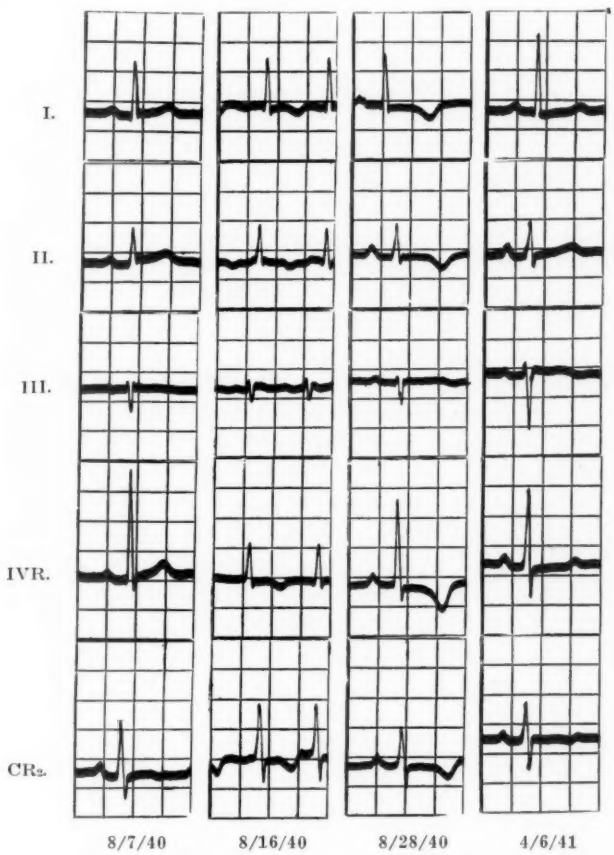

Fig. 4.—Sequence of electrocardiographic changes in Case 4.

CASE 5.—The patient was a physician, aged 38 years. In February, 1939, he had a "cold" and sore throat which were severe enough to confine him to his home for a few days, and for which some sulfanilamide was taken. About two weeks later he began to have general malaise and fatigue, followed, two or three days later, by pain in the chest which began gradually and was localized in a small region beneath the left nipple. The pain was moderately sharp, made the patient uncomfortable, and was aggravated by change in posture or by almost any body movement. There was no accentuation as a result of swallowing or deep breathing.

The pain persisted with varying severity for about four weeks, during which time the patient was confined to his home. There was no fever, and the leucocyte count and sedimentation rate were normal. He gradually improved to the point of general well-being, but there were occasional mild recurrences of the pain for the next four or five months. Roentgenoscopic and roentgenkymographic examinations and roentgenograms of the chest and heart gave negative results, except that a small pericardial plaque was noticed in September, 1940. From August, 1940,

to February, 1941, the patient felt exceptionally well and was free from pain. In March, a mild head cold developed, and a week later there was a recurrence of painful precordial distress lasting several hours. After this short attack the patient again became symptomless and was feeling well when last heard from (April, 1941).

In the early part of the patient's illness the diagnosis was left in abeyance; the possibility of occlusion of a small coronary vessel was suspected. The more complete development of the clinical picture, together with the evolution of the electrocardiographic pattern, seemed to indicate acute pericarditis, and, in retrospect, it is believed that the whole picture supports this diagnosis.

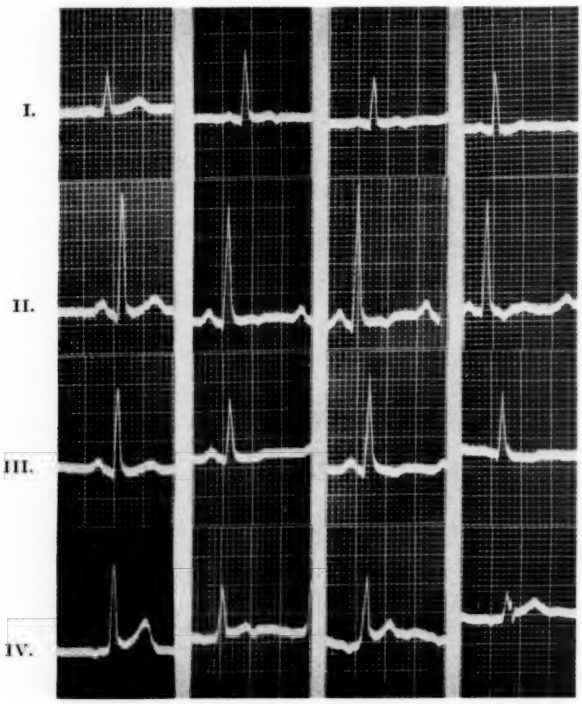

Fig. 5.—Sequence of electrocardiographic changes in Case 5.

The electrocardiograms (Fig. 5) showed early elevation of the S-T segment in Leads I and II and in the chest lead, and, later, negativity of the T wave in all the limb leads. The chest lead in this instance showed persistent elevation of the S-T segment. There was no Q or T pattern of coronary occlusion.

CASE 6.—A civil service worker, a man, aged 46 years, had sustained a fracture of the left tibia, followed by osteomyelitis, twenty-three years previously. The fracture had healed satisfactorily at that time. In September, 1940, an infection of the soft tissue of the left leg developed but responded to treatment by wet dressings and drainage. On Dec. 2, 1940, there was recurrence of cellulitis of the left leg, with fever, and the patient was referred to the hospital.

On this same evening there was a gradual onset of severe substernal pain, with extension to the interscapular region and throat. There was some cyanosis; the

patient's temperature was 102° F.; and he appeared ill. The condition was believed by the house physicians to be coronary occlusion. This diagnosis seemed to be supported by a convulsive attack with syncope, in the middle of the night. When the patient was seen by one of us, a definite pericardial rub was heard, and, because of the patient's fever, it was believed that the whole picture was compatible with acute pericarditis. This opinion was supported by electrocardiographic evidence, and, we believe, was fully substantiated later by the patient's clinical

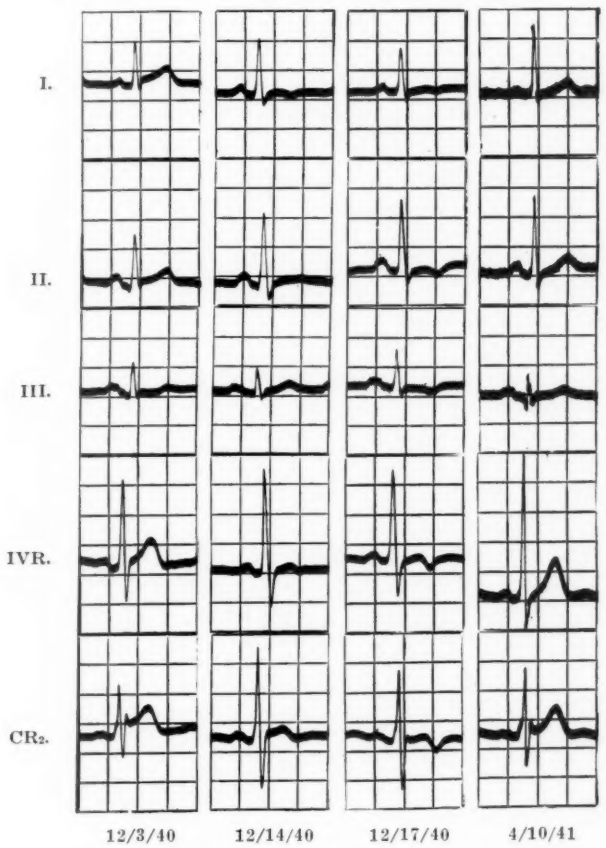

Fig. 6.—Sequence of electrocardiographic changes in Case 6.

course. He was under observation in the hospital for thirty days. During this period he had recurring attacks of precordial pain, periods of low-grade fever, and, at times, pain in the left shoulder tip at the onset of inspiration. During this time there was no leucocytosis, but the sedimentation rate was elevated persistently, averaging 63 mm. in one hour. The patient was given 60 to 75 grains (4 to 5 Gm.) of sulfathiazole daily for six days, with a questionable effect on the fever, and no evidence of general clinical improvement. During this time there was a slight, globe-shaped enlargement of the heart. On one occasion, when there was a recrudescence of the fever, we considered the advisability of doing a pericardial tap, fearing the onset of suppuration, but this was deferred and improvement spontaneously occurred.

During January, 1941, the patient continued to have ill-defined attacks of precordial pain but otherwise felt fairly well. He was allowed to return to work

in February and has continued to feel well except for occasional aching precordial distress.

The electrocardiograms (Fig. 6) showed the characteristic early elevation of the S-T segments, the late negativity of the T wave in all limb leads, and return of the electrocardiogram to normal.

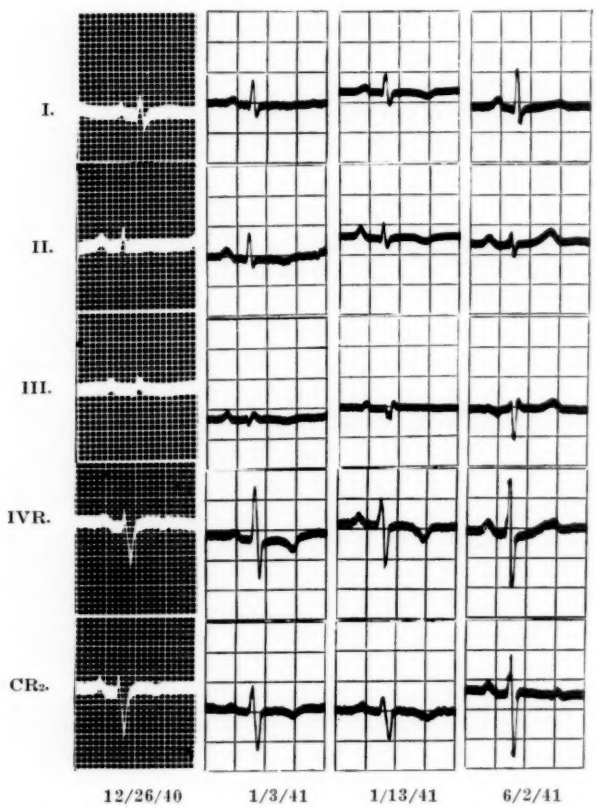

Fig. 7.—Sequence of electrocardiographic changes in Case 7.

CASE 7.—A man, aged 40 years, was admitted to the hospital Dec. 24, 1940, with the history that for the preceding ten days he had been in bed, feeling weak and having chills and fever. On the day of admission there had developed a dull, rather constant substernal pain which was not affected by respiration but was partly relieved when the patient lay on the right side. He appeared pale and ill; the pulse rate was rapid; and there was a loud pericardial friction sound. There had been no dyspnea previous to his coming to the hospital. The home physician had suspected coronary occlusion. The cardiac silhouette was considerably enlarged. The patient was observed in the hospital for four weeks, during the first week of which time there were low-grade fever, moderate tachycardia, and an increased sedimentation rate (30 mm. in one hour). No leucocytosis occurred. He was dismissed feeling well, and his cardiac silhouette was of normal size at that time. When seen last, in June, 1941, he appeared to be in excellent health, was working full time, and made no complaints. Examination of the heart gave negative results.

The series of electrocardiographic tracings (Fig. 7) showed gradual development of negativity of the T wave in all derivations, and, later, return of the tracing to

normal. The first tracings showed low amplitude of the QRS complexes in all three leads and isoelectric T waves but no elevation of the S-T segment. Whether the latter had occurred earlier in the disease would be impossible to say.

CASE 8.—A physician, aged 45 years, had a long history of previous illnesses, including repeated attacks of tonsillitis. In 1909 he was thought to have had pulmonary embolism after appendectomy. In 1921 he had scarlet fever, followed by rheumatism. In 1927, eleven days after the repair of a right inguinal hernia, sudden substernal pain developed, and it was believed that he had had pulmonary embolism. At this time a systolic click was heard, which later gave place to a pericardial friction rub. Low-grade fever persisted for twelve days. Definite saphenous thrombophlebitis occurred on the nineteenth postoperative day. Several electrocardiograms, taken at intervals of a month or more, did not reveal anything of diagnostic value.

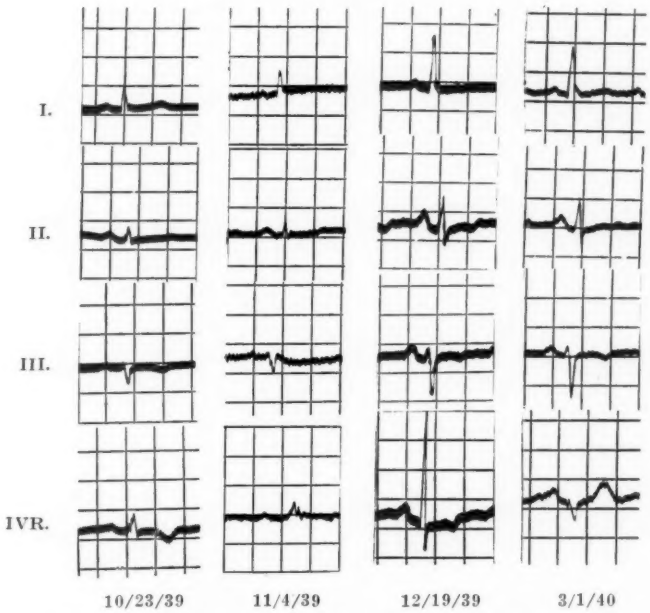

Fig. 8.—Sequence of electrocardiographic changes in Case 8.

The illness, during which we have complete electrocardiographic studies, began Oct. 1, 1939, as influenza and sinusitis; it confined the patient to bed and was associated with a temperature of 101° F. Between October 22 and November 6, he had several short attacks of auricular fibrillation and tachycardia and developed a dull retrosternal discomfort, which was increased by effort. In January, 1940, the patient was still experiencing the retrosternal pain on exertion, and it persisted for three to six hours after resting. In March he had a recrudescence of general malaise and low-grade fever and was in bed for ten days. After this, gradual improvement occurred, but there was still considerable general asthenia which responded slowly to a regimen of rest.

The electrocardiograms (Fig. 8) differed from those in the other cases in that they did not show any of the changes generally associated with acute pericarditis, but rather those of chronic pericarditis, namely, low amplitude and isoelectric or inverted T waves in all leads. The return toward normal in this series of tracings was particularly striking.

CASE 9.—A farmer, aged 52 years, registered at the clinic Jan. 14, 1930. He gave the history that on Oct. 7, 1929, he had suffered from dull pain in the epigastrium, associated with general malaise and low-grade fever. There was, at times, pain at the tip of the left shoulder, between the shoulder blades, and on both sides of the chest. There were orthopnea, weakness, sweats, and a heavy sensation in the chest. The pain and low-grade fever persisted intermittently for the next three months. Examination in the clinic in January gave negative results except for distant heart sounds. The leucocyte count, the results of roentgenoscopic examination, and the roentgenogram of the chest were normal.

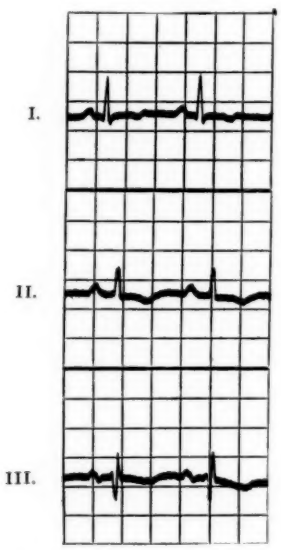

Fig. 9.—Electrocardiographic changes in Case 9.

The patient gradually improved in the hospital, although the diagnosis remained uncertain. Inasmuch as his pain had been accentuated by exercise, a true effort angina was suspected, and finally, because of his electrocardiographic abnormalities, a diagnosis of coronary occlusion was made.

In 1935 we obtained the information from the patient's home physician that since his visit to the clinic he had been exceptionally well and was working every day without any trouble. In July, 1941, he was still in good health, without any symptoms of heart disease, and, in retrospect, we believe that he had an attack of acute pericarditis in 1930.

The electrocardiogram (Fig. 9), taken in 1930, showed negativity of the T waves in the three limb leads, and we should consider the picture compatible with acute pericarditis in its later stages.

Two cases of pain in the chest simulated coronary occlusion, but this diagnosis is regarded as untenable; the series of electrocardiographic tracings indicated that the patients had pericarditis.

CASE 10.—A man, aged 25 years, while en route to work on April 22, 1940, became aware of substernal discomfort which rapidly progressed in severity. He was seen by his physician 1.5 hours after the pain began, at which time the results of physical examination and the blood pressure were normal. The pain was located in an area about the size of the hand, lying transversely over the xiphoid process.

It was described as a sensation of compression in the chest, was not projected, and was aggravated by the supine position and by inspiration. The discomfort was severe for about six hours but had disappeared completely within about eighteen hours. No friction rub was ever present during subsequent examinations, and fever, leucocytosis, and an increase in sedimentation rate did not occur. Three roentgenologic examinations of the chest in a short period after the attack gave negative results, and no abnormality in the cardiac silhouette was present. The patient recovered quickly, and, when last heard of through his home physician in April, 1941, he had remained completely well.

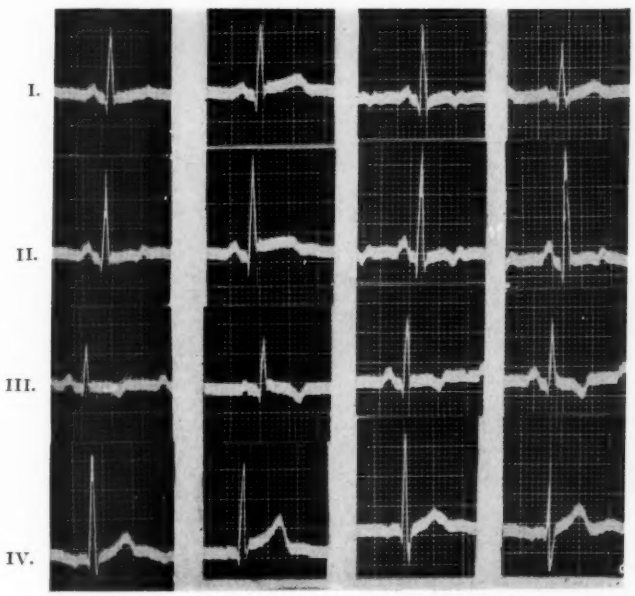

Fig. 10.—Sequence of electrocardiographic changes in Case 10.

The patient's physician made a provisional diagnosis of acute pericarditis, but, because of the obviously incongruous features of the attack, he wished our opinion on the electrocardiographic tracings, which are reproduced here.

The features which suggest pericarditis in the electrocardiographic tracings (Fig. 10) include the elevated R-T segments in the standard and precordial leads in the second tracing, the subsequent negativity of the T wave in the limb leads, and the tendency of the tracing to return to normal.

CASE 11.—The patient was a lawyer, aged 34 years, without history of previous illness. On Sept. 3, 1939, while he was driving, a dull intermittent, epigastric distress developed. This distress soon involved the lower part of the chest and an hour later became agonizing, with associated pain in the back of the neck. The pain was made worse by deep breathing. The patient was seen by his physician, who observed him, after two hours of severe pain, in apparent shock, and recorded a pulse rate of 110 and a temperature of 101.4° F. He was suspected of having coronary occlusion, was given 0.5 grain (0.032 Gm.) of morphine sulfate, and was moved by ambulance to the hospital. No history of friction rub was obtained.

The distress soon disappeared, and the patient wished to return home on the following day but was persuaded to rest in bed for six weeks. After this he felt

well and pursued an active life. On Jan. 21, 1940, he had pain across the lower part of his chest, was given 0.25 grain (0.016 Gm.) of morphine, and was kept in bed for one week. For the next two months there were occasional twinges of precordial pain and a sense of oppression in the left side of the chest when the patient was lying on the left side. He visited the clinic on March 6, 1940, where the results of general physical examination were negative; the blood pressure was 112/80. The electrocardiogram and the roentgenogram of the chest were normal. The patient returned to his normal life and full-time work, feeling well. When last heard from, in April, 1941, he had had no symptoms other than an occasional, fleeting, precordial discomfort.

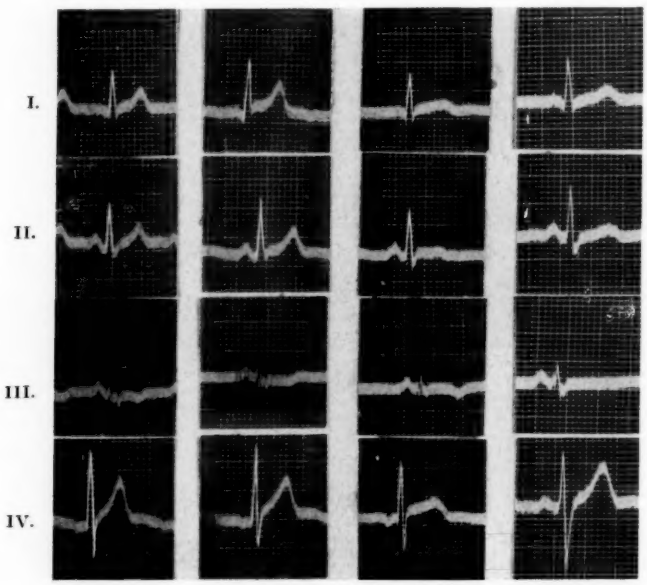

Fig. 11.—Sequence of electrocardiographic changes in Case 11.

The diagnosis of previous pericarditis rested almost wholly on our interpretation of the serial electrocardiograms which were taken after his attack of severe pain (Fig. 11). The elevation of the S-T segment in Leads I and II, with a convexity downward, accompanied by rather peaked T waves without any depression of the segment in Lead III, is believed to be indicative of some type of pericardial involvement. The electrocardiogram returned to normal within a few days, without anything to suggest a Q or T pattern of coronary occlusion. There was a questionable, slight diminution in the amplitude of the QRS complexes, and, in the third tracing, there was a dome-shaped T wave.

Three cases of pain in the chest suggested coronary occlusion; the correct diagnosis is believed to be acute pericarditis, but an associated coronary occlusion has not been absolutely excluded.

CASE 12.—A traveling salesman, aged 45 years, had had good health previous to his present illness, except for a mild illness in 1936 which lasted several months and was said to be accompanied by low-grade fever and some pleuritic pains.

On June 6, 1940, while he was driving, an aching pain developed in the right anterior part of the chest and extended into the right arm. The pain subsided but

recurred intermittently over the next week. When he was seen by his physician on June 10, examination gave negative results except for evidence of apprehension. The temperature was normal, and the leucocytes numbered 17,300 in each cubic millimeter of blood. The patient rested during the next six weeks and had only occasional pain in the right side of the chest. The blood pressure remained in the vicinity of 125/85 during this period. When he returned to work, August 1, he was still having occasional pain in the anterior part of the chest which came on with exercise and extended at times to both wrists; also, at times, he had a little "uneasiness" in the left wrist. On August 8, after his evening meal, more severe distress developed in the anterior part of the chest than he had experienced previously, and he vomited. On the following day the cardiac sounds were normal; the blood pressure was 98/76; and the temperature was 99.2° F. Hypodermic injections were given for relief of pain. Since then the patient has had recurring pain which begins in the right axillary region and spreads to the upper sternal region and arm. The pain occasionally lasts for hours, and the relief by rest has been indefinite.

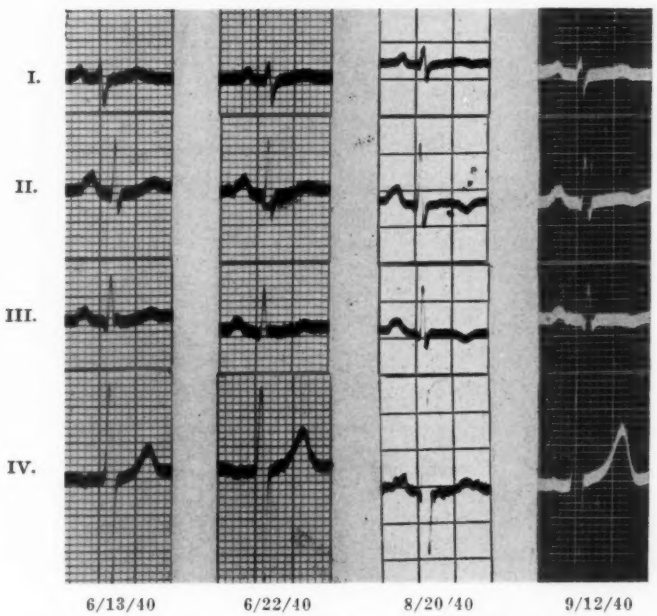

Fig. 12.—Sequence of electrocardiographic changes in Case 12.

In August, 1940, the patient was seen at the clinic, where the physical examination gave negative results; the blood pressure was 130/90, and the temperature was 99.2° F. The routine examination of the urine and blood and a roentgenogram of the chest showed nothing abnormal. The patient was encouraged to believe that he might not have coronary disease, and within a few weeks he had regained his normal health. When last heard from, in July, 1941, he was active, feeling well, and had had no pain in the chest for months.

The series of electrocardiograms (Fig. 12) did not show any abnormality during the early period of his illness. Later, negative T waves in Leads II and III and diphasic T waves in Lead I developed. These tracings are not of great diagnostic help but are believed to be compatible with the diagnosis of pericarditis.

CASE 13.—A farmer, aged 46 years, registered at the clinic in July, 1940, complaining of epigastric distress which was of two months' duration, a dull pain over the precordial region, and some exertional dyspnea of three weeks' duration. On a number of occasions in previous years he had been seen at the clinic for minor complaints, such as hay fever and furunculosis, and the results of previous examination of the cardiovascular system had been negative. The precordial pain was described as not extending to other regions, as continuing over a period of several days, and as not being accentuated by exertion. There was also the history of a paroxysm of irregular heart action, which suggested auricular fibrillation. On

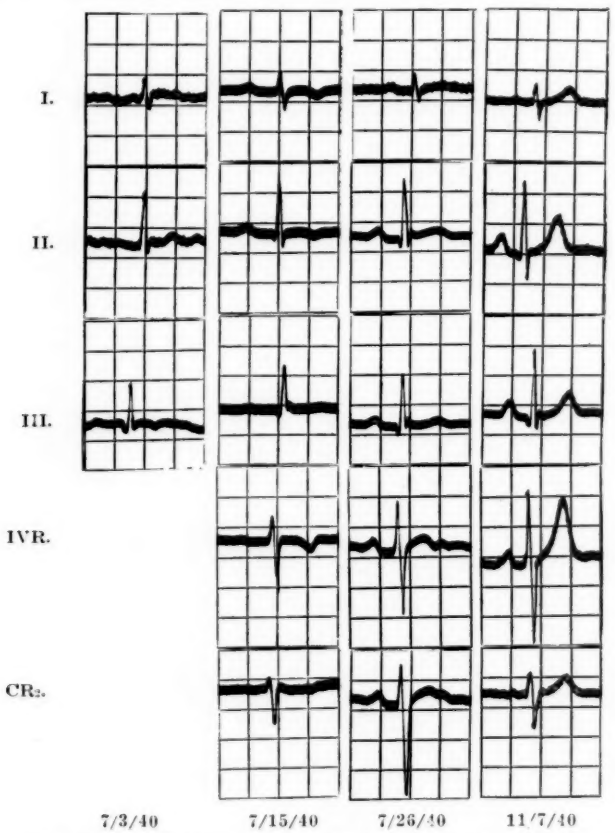

Fig. 13.—Sequence of electrocardiographic changes in Case 13.

physical examination the general condition of the patient seemed good, but there were a pericardial friction rub, slight enlargement of the liver, and moderate enlargement of the cardiac shadow. He was observed in the hospital for four weeks, during the first week of which there were low-grade fever, with temperatures up to 100° F., and an increased sedimentation rate (to 103 mm. in one hour). There was never any leucocytosis. Whether the pathologic process was acute pericarditis or coronary occlusion associated with pericarditis was uncertain for some time, but the rapid improvement of the patient and the sequence of events in the electrocardiograms firmly established the diagnosis of pericarditis, in our opinion. The patient was dismissed feeling well, and, when he was seen again in November, 1940, his cardiac status was considered to be that of a normal person. In July, 1941, he was feeling well and working full time in the harvest fields.

The electrocardiograms (Fig. 13) showed elevation of the S-T segment in the early tracing, followed by negativity of the T wave in subsequent tracings, but, interestingly, there was a second phase of elevation of the S-T segment, with dome-shaped T waves. The complete return of the tracing to normal occurred in three months' time.

CASE 14.—A woman, aged 60 years, whose past medical history was not noteworthy, other than for cholecystectomy, was seen at the clinic in December, 1923. In October, 1923, a sense of pressure had developed in the chest, with severe pain down the arms which lasted about an hour, and which was associated with nausea and diarrhea. There was mild pain in the anterior part of the chest for the following five days, and the home physician made a diagnosis of pericarditis. On examination at the clinic two months later, the patient was feeling fairly well and had only slight dyspnea on occasion. A diagnosis of coronary sclerosis and previous coronary occlusion, with myocardial infarction, was made. The outstanding feature of the electrocardiogram was negativity of the T waves in all three leads. When the patient returned to the clinic in 1924 and 1926, she gave a history of no further chest pain and no dyspnea. In March, 1941, her attending physician wrote that she was feeling well, although she was having increasing shortness of breath and edema of the ankles.

It may be questioned whether we are justified in including this case, as it may represent only a long survival after acute occlusion. However, the suggestive electrocardiographic tracing, together with the long history of freedom from pain in the chest, tempts us to believe that the attack of pain in the chest in 1923 might have been due entirely to acute pericarditis.

COMMENT

We do not assume that these patients had identical pathologic processes, but we do believe that in each case we were dealing with pericarditis, probably inflammatory in nature and infectious in origin. In support of the latter view was the history of a recent antecedent infection in many of the cases. Although the correct diagnosis in the cases here presented depended, we believe, chiefly on the correct interpretation of the associated electrocardiographic changes, there were numerous clinical characteristics of importance in the differential diagnosis. It is well known that inflammatory diseases of the pericardium may be completely painless, but it is in a small group of patients with pain sufficiently severe to suggest the possibility of coronary occlusion that we are particularly interested. The question whether, in some of these cases, there might have been evidences of rheumatic fever may be raised, but we consider this an unlikely possibility. Neither do we believe that these patients had a tuberculous process, although we occasionally have observed young adults with a benign, apparently self-limited form of pericarditis which may possibly have been caused by tuberculosis. None of the patients reported in this series had any evidence of an active focus of tuberculosis in the chest or lymph nodes or previous illnesses of a tuberculous nature.

It is a question whether these patients will have further recurrences of pericarditis, and whether constrictive pericarditis may develop. The former we consider possible in some instances, but the latter is unlikely.

In two cases, the type of pain was similar to that of the patients with spontaneous mediastinal emphysema reported by Scott[1] and by Hamman,[2] but, since the series of electrocardiographic tracings were so characteristic of pericarditis, we believe that the latter is more likely. These two cases were different from the group in general because of the absence of preceding infection, the intense severity but short duration of the pain, the absence of fever, rub, or cardiac enlargement, and the rapid return to health without any further distress in the chest.

Clinical Features of Acute Pericarditis in Adults.—The age incidence in the group of patients presented extends over a very wide range but tends to average lower than for patients with coronary occlusion. Averages may be misleading, but the average age of patients who have coronary occlusion is about 55 years, as compared with 42 years in our group of patients.

As previously mentioned, there was a history of some acute infection, usually in the upper part of the respiratory tract, preceding the attack of pain in the chest in 57 per cent of these cases. Of the first group of nine cases, in which the diagnosis seems established, preceding infection was present in all but one. Such a frequency of preceding acute infection is not observed among patients suffering from attacks of coronary thrombosis.

The pain in acute pericarditis shows certain differences from that of acute coronary thrombosis. It is seldom described as agonizing, is in general less severe, and less often requires morphine for relief. It is frequently intermittent, and there may be short premonitory paroxysms, unrelated to exertion, preceding the attack of severe pain which forces the patient to request medical care. The pain usually is located in the substernal and epigastric regions, but, in a few instances, it has been localized curiously over a small precordial area well to the left of the midline. The pain rarely extends to other regions, but, in some instances, there may be unilateral or bilateral pain in the shoulder tip, or diffuse pains in the sides of the chest and back. Deep breathing, rotation of the trunk, or swallowing may aggravate the pain. In some instances the history indicated that the patient was most comfortable in the sitting position, leaning forward. Although exertion may produce the pain, frequently it will be found to be due to flexion or twisting of the trunk, and the distress may persist for hours after the exertion ceases. Long after recovery from the acute phase of the disease, the patient may experience attacks of pain in the chest of variable location and duration, without reference to exertion.

Febrile reactions, in which the temperature reaches 101° F. or more, are much more likely to occur with infectious pericarditis than with myocardial infarction. Sharp febrile reactions, particularly if they respond rapidly to treatment with sulfonamide drugs, as in Case 1, speak for an infectious origin of the pericardial reaction.

In some cases of pericarditis the cardiac silhouette may be increased considerably in size. Such degrees of cardiac enlargement are unusual in acute myocardial infarction. Consequently, if a huge cardiac silhouette is observed roentgenographically, it favors the diagnosis of pericarditis rather than that of coronary occlusion. In the majority of these cases in which pain has been the outstanding feature, there has been little or no enlargement of the cardiac shadow, but in three cases there was moderate enlargement, with a return to normal when the patient recovered.

In the cases which we have been able to follow very closely, the sedimentation rate frequently has been an index of the presence of an infection, and only rarely has there been any elevation of the leucocyte count. Other laboratory examinations usually gave negative results.

Electrocardiographic Features of Acute Pericarditis.—The electrocardiographic distinction between acute pericarditis and acute coronary occlusion depends on two things. First, it implies complete familiarity with the pattern of changes in the standard and precordial leads which are produced by myocardial infarctions in various locations. Of course, it must be admitted that infarctions of unusual location or size, or multiple infarctions, occasionally produce electrocardiographic changes that cannot be classified. Second, it is necessary to understand the various general patterns of electrocardiographic changes that are produced by acute and subacute pericarditis.

The Q_1-T_1 and Q_3-T_3 changes in anterior and posterior infarction of the left ventricle are well known[3] and need no comment. We recognize many variations from these patterns which, if they occur in a serial manner after an attack of pain in the chest, will support a diagnosis of coronary occlusion. The electrocardiographic changes described by Wood and his associates[4] in infarction of the lateral wall may become established, in time, as another characteristic pattern.

Experimental and clinical evidence indicates that one of the most characteristic modifications of the electrocardiogram produced by pericarditis is upward displacement of the RS-T segments in the standard leads.[5-9] This is most characteristic if elevation occurs in all of the standard leads, although it may occur in Leads I and II, or almost exclusively in Lead I. The R-T of the elevated segment either is concave upward or forms a straight line from its origin in the R wave to the crest of the T wave. This is to be contrasted with the upward convexity of the elevated R-T segment in coronary occlusion. Reciprocal deviations of RS-T segments in Leads I and III, such as may occur after acute coronary occlusion, rarely occur in uncomplicated pericarditis. The T waves in acute pericarditis primarily tend to undergo one of two changes; they may become exaggerated in amplitude or sharply peaked, or they may be rounded, with a dome shape.

Very shortly the segment displacement is diminished or disappears altogether, and negativity of the T wave appears. In most instances, if frequent electrocardiograms are taken, there is a stage in which the T waves become negative in all of the standard leads. This in itself is suggestive of pericarditis, although it may be seen after acute coronary occlusion or after a second acute coronary occlusion. In the latter cases, the T waves usually have a shape which suggests coronary disease; the QRS often is deformed, particularly by notching; and the precordial lead may exhibit changes indicative of coronary occlusion.

The changes in the apical precordial lead are more difficult to classify. The S-T segment may duplicate the elevation observed in S-T_1, but this is not common. The T wave in this lead may become exaggerated and sharp. At the stage of inversion of the T wave in the standard leads the T wave in IVR and IVF usually is inverted, although it may only lose voltage. Rarely is the R wave less than 2 mm., and usually it is of normal size, which assists in the exclusion of anterior infarction of the left ventricle. In no instance has a Q wave in the apical lead appeared in known acute pericarditis.

In acute pericarditis, Q and T patterns, such as occur in early or late myocardial infarction, are not observed. Loss of R in the apical lead and the appearance of a large Q in this lead, which changes are frequently associated with anterior infarction of the left ventricle, do not occur.

Occasionally (Case 8) the pericarditis appears to be more of a chronic or subacute variety, in which case low voltage of the QRS and T waves is the striking abnormality of the electrocardiogram. As recovery occurs, improvement in voltage is one of the first signs of electrocardiographic change. Under such circumstances, minor electrocardiographic changes may persist for weeks or months after the patient has regained his normal health.

Within one to six weeks after the more acute phase of pericarditis subsides, the electrocardiogram returns to normal or begins to approach normal limits. There are no traces of the Q or T pattern in the standard leads and no persistence of Q or absence of R in the precordial apical leads to suggest a previous occlusion. Aside from this lack of residua of acute myocardial infarction, this tendency to a rapid return toward normal is one of the most important features of the electrocardiogram in acute pericarditis and distinguishes it from that of coronary occlusion, which tends to be reflected by recognizable changes for a much longer period. This also emphasizes the great importance of a series of electrocardiograms in arriving at the correct diagnosis.

There remains the differentiation between acute pericarditis and coronary occlusion complicated by pericarditis. The distinction usually can be made because coronary occlusion, even though it may be complicated by pericarditis, will reveal itself by T or Q patterns in the

standard leads or by the appearance of a large Q wave or the absence of an R wave in the apical precordial leads.

It is to be emphasized that this is a select group of patients with a disease which is rare in comparison with the number of patients we have seen who had coronary occlusion within the same period. The outlook for these patients is entirely different, we believe, from that of patients with coronary disease. The decision that a patient has acute coronary thrombosis imposes a grave immediate prognosis, a guarded ultimate prognosis, a prolonged convalescence, and a permanent modification of the patient's way of living. A diagnosis of acute pericarditis warrants a good immediate and remote prognosis and a period of convalescence less prolonged, on the average, than that demanded by acute coronary thrombosis, and allows the patient to resume his normal life after recovery from the attack.

SUMMARY

Fourteen cases are presented, together with evidence which we believe justifies a diagnosis of acute infectious pericarditis, rather than acute coronary occlusion. Because of the nature and location of the pain, coronary occlusion had to be considered. In several instances in which a friction rub was heard, the natural inclination was to make a diagnosis of acute pericarditis, until the electrocardiographic changes confused the issue. The clinical and electrocardiographic grounds on which we have concluded that the correct diagnosis in each of these cases was acute infectious pericarditis have been stated.

In these cases the disease uniformly ran a benign course, with good recovery and without any evidence of significant impairment of cardiac function. Time alone will tell whether, in any of these cases, the disease will go on to the development of constrictive pericarditis, although we do not believe that it will. We have not found it necessary to impose any restriction on the normal activity of these people after the lapse of the few weeks to two or three months which were required for recovery. The indefinite pain in the chest which was observed occasionally in these persons subsequent to their acute attacks has not been accompanied by any demonstrable cardiac abnormality, has not been productive of any signs of myocardial insufficiency, and does not appear to nullify the good prognosis given to these patients.

Although none of these diagnoses was verified by post-mortem studies, the observations on the characteristics of the electrocardiographic changes which are seen in pericarditis are based on the results of investigations on pericarditis in animals and in other cases of pericarditis in man in which post-mortem studies were made.

It is our belief that this is an important problem. If our thesis is correct, there must be occasional instances in daily practice in which a lack of appreciation of the distinctions made here results in mistaking acute pericarditis for acute coronary occlusion. It is of the utmost

importance that such a mistake be avoided, because the immediate and ultimate prognosis and the program of future restrictions in the two conditions are so utterly different that great injustice to the patient may result from failure to make the correct diagnosis.

We have many acknowledgments to make to physicians who cooperated with us by sending electrocardiograms and details of the illnesses of many of these patients. We must mention, in particular, the following: Dr. Young, Duluth, Minn.; Dr. Hiett and Dr. Howell, Fort Worth, Texas; Dr. Kurtz and Dr. Lustok, Milwaukee, Wis.; Dr. Scherer and Dr. Fahr, Minneapolis, Minn.; Dr. Nickel, Bluffton, Ind.; Dr. Matthews, Shreveport, La.; Dr. Berger, Cleveland, Ohio; and Dr. Langston, Oklahoma City, Okla.

REFERENCES

1. Scott, A. M.: The Significance of the Anginal Syndrome in Acute Spontaneous Pneumomediastinum, Lancet **1**: 1327, 1937.
2. Hamman, Louis: Spontaneous Mediastinal Emphysema (Henry Sewall Lecture), Bull. Johns Hopkins Hosp. **64**: 1, 1939.
3. Barnes, A. R.: Electrocardiographic Patterns, Springfield, Ill., 1940, Charles C Thomas.
4. Wood, F. C., Wolferth, C. C., and Bellet, Samuel: Infarction of the Lateral Wall of the Left Ventricle: Electrocardiographic Characteristics, AM. HEART J. **16**: 387, 1938.
5. Burchell, H. B., Barnes, A. R., and Mann, F. C.: The Electrocardiographic Picture of Experimental Localized Pericarditis, AM. HEART J. **18**: 133, 1939.
6. Noth, P. H., and Barnes, A. R.: Electrocardiographic Changes Associated With Pericarditis, Arch. Int. Med. **65**: 291, 1940.
7. Bellet, Samuel, and McMillan, T. M.: Electrocardiographic Patterns in Acute Pericarditis; Evolution, Causes and Diagnostic Significance of Patterns in Limb and Chest Leads; a Study of 57 Cases, Arch. Int. Med. **61**: 381, 1938.
8. Vander Veer, J. B., and Norris, R. F.: Electrocardiographic Changes in Acute Pericarditis, J. A. M. A. **113**: 1483, 1939.
9. Winternitz, Max, and Langendorf, Richard: Das Elektrokardiogramm der Perikarditis, Acta med. Scandinav. **94**: 141, 1938.

DISCUSSION

DR. GEORGE HERRMANN, Galveston, Texas.—The diagnostic electrocardiographic patterns worked out by Dr. Barnes are indeed very important, but require expert interpretation. The clinical diagnosis, even with the electrocardiographic studies, is not always as easy as one might think from his presentation. Some of us have seen cases in which a diagnosis of acute pericarditis was made, and later evidence developed which showed definitely that the acute pericarditis was really pericarditis epistenocardia. This was of particular importance in two cases in which pericardiectomy was contemplated, but in which, fortunately for the surgeon, death came suddenly on the eve of the operation; autopsy revealed that the abnormal pericardium was adherent to the thin scar of ventricular aneurysm. That impressed me with the fact that we must not go to the other extreme and make a diagnosis of simple pericarditis in instances in which pericarditis epistenocardia has developed. This must be kept in mind when patients have constrictive symptoms for the relief of which cardiac decortication is being considered.

DR. AARON ARKIN, Chicago.—We not infrequently see, in the hospital, young patients with acute pericarditis. A large percentage of the cases are tuberculous in nature. The diagnosis is not difficult when rheumatic heart disease can be excluded. These patients have an enlarged heart shadow which often recedes rapidly after a few weeks of bed rest. Roentgenologic examination often reveals a definite enlargement of the hilar lymph nodes, occasionally with some calcification.

This kind of collateral inflammatory tuberculous pericarditis is not serious and is caused by the close contact of a tuberculous lymph node with the pericardium.

The patient, usually a young person, complains of cardiac pain. Dyspnea may or may not be present. In the early stage a pericardial rub may be found. The heart shadow is often greatly enlarged by the effusion, which may be serous, serofibrinous, or hemorrhagic.

I do not believe that we should confuse these cases with those of acute coronary occlusion. The patients have few or no symptoms, sometimes not even dyspnea. One is astonished to find the enlarged area of dullness which shifts at the base with change of position. The electrocardiogram shows the usual changes which are caused by pericarditis.

The lymph nodes in contact with the pericardium may also cause an associated pleural effusion. The prognosis is good. Such a pericardial effusion, which is often without tubercle formation, is not a serious disease. In a few weeks the cardiac shadow may return to normal.

Dr. Joseph B. Vander Veer, Philadelphia.—We have had experiences at the Pennsylvania Hospital which are rather similar to those of Dr. Barnes and agree that this disease is not infrequently mistaken (from the electrocardiographic standpoint) for myocardial infarction. During the past few months we have seen three patients whose electrocardiographic changes had been interpreted as being due to myocardial infarction, but careful analysis of the record suggested that they were caused by acute pericarditis. This was subsequently borne out by other records and the clinical course of the patients.

One thing Dr. Barnes did not stress is that hemopericardium frequently produces the electrocardiographic pattern of acute pericarditis. The inflammation produced by the blood extends to the subepicardial myocardium in different areas of the ventricles and gives rise to the elevated RS-T segments. We have seen two patients of this type. At autopsy one of them, a youngster about 18 years of age with an unrecognized congenital lesion of the aorta, had a small rupture, with hemopericardium, although death did not occur for several days. The other patient had an aortic aneurysm, with oozing of blood into the pericardial sac for several days before the final rupture.

Our results in pericarditis bear out Dr. Deeds' observations on the chest leads. There is no one precordial lead that is best for all conditions. (Slide) I believe this slide illustrates well the variations one may get in the chest leads. It is typical of acute pericarditis. There are elevations of the RS-T segments in all of the CR leads, most marked in CR_4 and CR_5. The CF leads, however, show no significant changes, and Lead V (Wolferth and Wood) and Lead IVB show no changes. CL leads were also done and were similar to the CF leads in this case.

So, in this instance again, although the limb leads may be sufficient, it is helpful to have changes in the chest lead which may aid in confirming the diagnosis.

Dr. Louis N. Katz, Chicago.—In 1928, Dr. R. W. Scott, Dr. Harold Feil, and I were the first to describe this typical electrocardiographic pattern in a case of hemopericardium. Two years ago, Dr. R. Langendorf, of Prague, came to work at the Michael Reese Hospital and renewed my interest in the subject because he was enthusiastic about the studies he and his colleagues had made on this electrocardiographic feature. They had described, independently of Barnes, a similar electrocardiographic pattern in pericarditis. Since Dr. Langendorf has been with me, we have seen about half a dozen cases in which the characteristic electrocardiographic changes were present. The clinical manifestations noted by Dr. Barnes were also present in our cases.

DR. MAURICE S. JACOBS, Philadelphia.—One of the points that Dr. Barnes mentioned, but did not stress, was the character of the pericardial friction rub—not so much the character as the length of time that it lasts. It has been our impression that the pericardial friction rub, as it occurs in acute myocardial infarction, is of short duration. In short, in myocardial infarction one frequently does not hear a pericardial friction rub. It has been our opinion that this is due to the fact that the patient is not examined often enough. By that I mean not just once a day, but sometimes three or four times a day. One frequently hears a pericardial friction rub, for example, at seven o'clock at night which was not there in the afternoon or might not be there at midnight.

Ten years ago we pointed that out in a case of acute myocardial infarction in which, the third day after that infarction, the pericardial friction rub appeared at about seven o'clock at night and was gone by midnight. The patient had been examined twice before that day. I believe this is something that ought to be kept in mind.

DR. ARLIE R. BARNES, Rochester, Minn.—I subscribe to what Dr. Herrmann has said, namely, that we must not become overenthusiastic about pericarditis, but still I believe that we have been too prone to diagnose coronary thrombosis without sufficient consideration of other possibilities.

I was interested in what Dr. Arkin had to say about tuberculous pericarditis. We have seen it occasionally, but not in patients as old as those in this group.

Dr. Burchell and I had an interesting discussion concerning heart size. I have seen many cases of pericarditis in which the heart became large very rapidly, and I am convinced that in some of these cases we are dealing with the finest examples of acute dilatation of the heart which are known to clinical medicine. The enlargement is ordinarily ascribed to the accumulation of fluid in the pericardial sac, but I have had occasion to tap the pericardial sac as many as three times without obtaining any fluid whatsoever. Therefore, I believe that dilatation of the heart may occasionally be an important feature of acute pericarditis.

We have had the same experience as Dr. Vander Veer, namely, that hemopericardium will produce the same electrocardiographic changes that we have just described.

I am grateful to Dr. Jacobs for mentioning the duration of the friction rub, for it is true that in cases of pericarditis the rub persists for days, and sometimes as long as two weeks, whereas it may be transitory in acute myocardial infarction. In the making of the differential diagnosis, the electrocardiogram becomes the final arbiter, and one must be able to distinguish between the electrocardiographic mutations in pericarditis and those in acute coronary occlusion.

Department of Clinical Reports

SINOAURICULAR BLOCK AND RETROGRADE AURICULAR CONDUCTION IN A CASE OF PERMANENT COMPLETE HEART BLOCK

BRUNO KISCH, M.D., AND GARY ZUCKER, M.D.
NEW YORK, N. Y.

CASES of obvious sinoauricular block have seldom been recorded, although some authors state that they are probably more frequent than is supposed.[1-6] However, medical literature does not contain any instance in which sinoauricular block was associated with permanent complete heart block. For this reason we wish to record such a case.

In 1902, Mackenzie[7] first suggested that such a thing as sinoauricular block may occur, and, in 1907, Wenckebach[8] first described it fully. Levine[1] reported eighteen cases up to 1916, and Barlow[9] collected thirty-six between 1916 and 1926. Sinoauricular block may be caused by a disturbance in the node produced by humoral or nervous influences, or it may result from an organic disorder. No complete histologic study of the sinoauricular node has been made in any of these cases.

Included among those who believe that sinoauricular block is a functional disturbance is Smith,[2] who reported eight children with this condition. Of these, six were convalescent from diphtheria, whooping cough, or mumps. Zárday[10] described two cases, in one of which there was a brain tumor; in the other there was a Wenckebach block of both the sinoauricular node and the auriculoventricular node. Barlow[9] recognized the frequent association of sinoauricular block with a prolonged P-R interval. He could find no definite etiology, but implicated such factors as digitalis, salicylates, tobacco, infections, coronary sclerosis, and rheumatic heart disease. He noted that atropine usually abolished the block temporarily and concluded by saying that sinoauricular block was a "physiological" disturbance. Feldman[11] reported the case of a man with syphilitic heart disease and aortic insufficiency who had a prolonged P-R interval and occasional sinoauricular block. The latter increased after right carotid sinus stimulation and disappeared after the administration of $\frac{1}{75}$ grain of atropine sulfate.

From the Department of Experimental Medicine, Beth Israel Hospital, New York.
Received for publication Aug. 26, 1940.

Against the above opinion are the statements of Levine,[1] White,[3] Lewis,[4] Wallace and Katz,[5] and Van Buchem,[12] who look upon sinoauricular block as "pathological." They stress the fact that, in a majority of the cases which have been reported, there was evidence of arteriosclerotic, rheumatic, or syphilitic heart disease, a history of convalescence from a severe infection, the presence of defective auriculoventricular conduction, or previous administration of digitalis. Wallace and Katz[5] reported a case of sinoauricular block in which there was not only prolongation of the P-R interval, but also occasional dropping of a ventricular beat.

CASE REPORT

J. G., a 64-year-old white man, was admitted to the service of Dr. I. W. Held, at Beth Israel Hospital, on Dec. 19, 1939, because of the sudden onset, two weeks prior to admission, of dizziness and substernal pain which lasted two minutes. Several hours later, while walking home, the patient experienced vertigo, followed by unconsciousness for about three minutes. There were no symptoms thereafter until three days before entry, when he became dizzy and vomited several times. For the preceding two years he had experienced moderate dyspnea, and an aching substernal pain, which occasionally radiated to the left shoulder, was induced by exertion, and was relieved by one to two minutes' rest. There had been no orthopnea, nocturnal dyspnea, palpitation, edema of the ankles, or known hypertension. There was no history of syphilis. An electrocardiogram, taken at home the day preceding admission, showed complete heart block.

Physical examination revealed a well-nourished and well-developed elderly man who was slightly cyanotic but not dyspneic. The patient was alert, oriented, and cooperative. The neck veins were not distended. The pupils were equal and regular and reacted well. The optic discs were well outlined; the retinal veins were full and tortuous; and the arteries were thin. The lungs were normal. The apex impulse of the heart could not be felt. The rhythm was regular. The ventricular and pulse rates were 30 per minute. The sounds at the base of the heart were barely audible, but at the apex they were of fair quality. There were no murmurs. The blood pressure was 120/54. The liver was felt 2 to 3 fingerbreadths below the costal margin. The spleen was not felt. There was no peripheral edema. Bilateral inguinal hernias were present. The prostate was slightly enlarged but was smooth.

Laboratory Data.—The specific gravity of the urine was 1.010 to 1.018; the urine contained a trace of albumin, and an occasional cast and leucocyte. On admission, the erythrocyte count was 5,210,000; the hemoglobin, 105 per cent (Sahli); and the leucocyte count, 14,300, with 79 per cent polymorphonuclear cells. The sedimentation rate was 4 mm. in forty-five minutes. The venous pressure was 14 cm. of blood. The blood Wassermann, Kline, and Kahn reactions were negative. The blood glucose was 105 mg. per cent, and the nonprotein nitrogen was 120 mg. per cent.

Course.—A diagnosis of arteriosclerotic heart disease with complete heart block and Morgagni-Adams-Stokes syndrome was made. The pulse rate varied between 22 and 32, without therapy. Movement in bed caused dizziness and weakness; nausea was constant. Adrenalin increased the pulse rate and lessened the symptoms. The patient's illness was complicated on the sixth day in the hospital by a massive hematemesis, probably from a peptic ulcer. During the twentieth and twenty-first days in the hospital, Jan. 7 and 8, 1940, he had several severe attacks of Morgagni-Adams-Stokes syndrome, with convulsions and unconsciousness, asso-

ciated with ventricular standstill for seven to ten seconds. Adrenalin, given hypodermically, produced relief. On the twenty-second day the patient had an acute perforation of a gastric ulcer, for which laparotomy and simple closure were performed. The patient was fully digitalized with digifolin intramuscularly because of signs of early congestive failure. His postoperative condition was never good. The heart rate was 44 per minute. The patient presented the clinical picture of peripheral circulatory collapse, with a blood pressure of 80/40. Death occurred suddenly on the second postoperative day.

Principal Pathologic Observations.—The outside configuration of the heart was normal. No endocardial lesions were seen. The coronary arteries, in general, were normal in size. The endocardium of the left ventricle was slightly opaque and thickened. A transverse incision 1.2 cm. below the base of the posterior aortic cusp, slightly behind its middle, revealed a somewhat butterfly-shaped scar which, in its posterior portion, was separated from the endocardium by a thin layer of myocardium which appeared grossly intact. A parallel incision 6 mm. below this one showed only traces of discoloration in the myocardium. In the lower portion of the left ventricular wall, a few grayish-white areas, up to 1 cm. in diameter, were seen. There seemed to be a number of much smaller ones. The wall of the left ventricle, halfway between base and apex, measured without the trabeculae, was 2.2 cm. thick; that of the right ventricle measured 3.5 mm. The right auricle, particularly in the region of the sinus node, showed nothing unusual. After continued fixation, an irregularly purplish field, measuring 1.1 cm. transversely and 0.9 cm. sagittally, became visible in the region of the sinoauricular node. It contained a small, round, darker, red spot. Longitudinal section of this region showed a corresponding subendocardial area which appeared more purplish and yellowish than the surrounding myocardium. The ascending aorta was slightly larger than normal; its intima was smooth.

Microscopic Observations.—No complete serial examination of the conducting system could be made. In the region of the large scar in the upper portion of the interventricular septum, fibrotic destruction of the septum was found. The destruction, in irregular fashion, permeated the whole thickness of the septum. In view of the fact that this large lesion must have severely affected either the lower part of the common trunk or the uppermost portions of the right and left branch of the bundle, it seemed reasonable to regard the multiple areas of subendocardial atrophy in both ventricles as a degenerative process in the ramifications of the bundle of His. Sections from the region of the sinoauricular node showed widespread atrophy and fibrosis of the muscular tissue which, perhaps, included damage to the node.

Summary of Pathologic Observations.—The pathologic changes were (1) moderate sclerosis of the coronary arteries (without narrowing of the major branches), (2) a scar in the upper portion of the interventricular septum, and (3) atrophy of the muscular tissue in the region of the sinoauricular node.

Electrocardiographic Observations.—Tracings were taken on ten different days. The following are the outstanding observations: (1) The A-V block was always complete, even on long tracings. (2) Sinoauricular block was present on five different days. This diagnosis was established by the occasional absence of a P wave in the presence of a fairly constant P-P interval (± 0.02 sec.), and by the fact that the interval between the P wave preceding and the one following the dropped P wave was double the usual P-P distance (Fig. 1). (3) Inverted P waves were seen after certain idioventricular contractions on four different days. They were interpreted as retrograde auricular contractions similar to those previously recorded by Cohn and Fraser,[13] Wilson and Robinson,[14] Danielopolu and Danulesco,[15] Barker,[16] Wolferth and McMillan,[17] and Kline, et al.[18a] (Fig. 1).

ANALYSIS OF OUR DATA ON SINOAURICULAR BLOCK

Analysis of the electrocardiograms revealed that the dropped P waves occurred only within an interval which extended grossly from the final deflection of the QRS complex to a point on the upswing of the T wave.

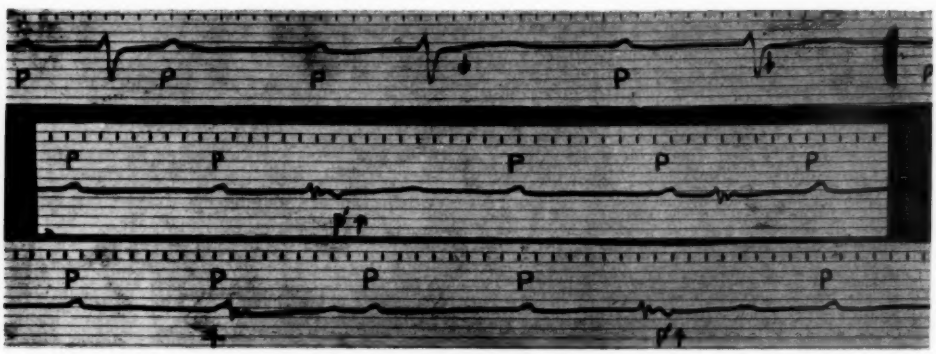

Fig. 1.—Tracing *1* (Dec. 28, 1939) shows S-A block after the second and third idioventricular beats. The arrows indicate the locations of the dropped P waves (R-P intervals of 0.30 sec. and 0.15 sec., respectively). The first idioventricular beat precedes the next P wave by 0.40 sec., and no S-A block takes place. The P wave is superimposed on the T wave. Time marked in 0.10 sec.

Tracings *2* and *3* are continuous (Jan. 7, 1940) and show retrograde auricular contractions (*P*) after the first and fourth idioventricular beats. The arrows mark the site of the normal sinus discharge.

P waves superimposed upon the QRS complex and the latter part of the T wave could be discerned readily (Fig. 1). The sinoauricular block in our case was not part of a Wenckebach period of the sinus node, because we were unable to detect any regular prolongation of the P-P interval preceding the dropped P wave. Furthermore, the relationship of the sinoauricular block to the preceding idioventricular contraction was not a coincidence dependent upon a chance phasic rhythm between the auricles and ventricles, for the sinoauricular block was observed when the auricular rate varied between 60 and 91, and the ventricular rate, between 24 and 41. The invariable relation of the dropped beat to the idioventricular contraction led us to conclude that the latter was indirectly responsible for the appearance of sinoauricular block in this case. The most probable explanation is that there was a temporary increase in vagal tone associated with each ventricular systole. During the prolonged diastole of the ventricles the aortic pressure fell markedly; then the large stroke volume of each systole caused a sharp stimulation of the carotid sinus and aortic depressor nerves which resulted in an increase in the vagal tone and a decrease in sympathetic tone.[18b] Ashman and Gouaux[19] and Kisch[20] have shown that striking alterations in vagal tone do occur with each ventricular systole in cases of complete heart block.

The data from all of the electrocardiograms which were taken on five different days are summarized in Table I. When the R-P interval was 0.00 to 0.10 sec., sinoauricular block never occurred; when it was

0.11 to 0.12 sec., sinoauricular block appeared three out of seven times; when it was 0.13 to 0.39 sec., sinoauricular block always occurred; when it was 0.40 to 0.42 sec., sinoauricular block was seen only two out of thirteen times; and, finally, when it was 0.43 to 1.00 sec., sinoauricular block never occurred (111 instances). If a vagal reflex were an important factor in the block in our case, the latter should have

TABLE I

THE RELATIONSHIP OF THE R-P INTERVAL TO THE FREQUENCY OF OCCURRENCE OF S-A BLOCK

R-P (SEC.)		0.00-0.10	0.11-0.12	0.13-0.39	0.40-0.42	0.43-1.00
S-A block	Present (no.)	0	3	51	2	0
	Absent (no.)	11	4	0	11	111

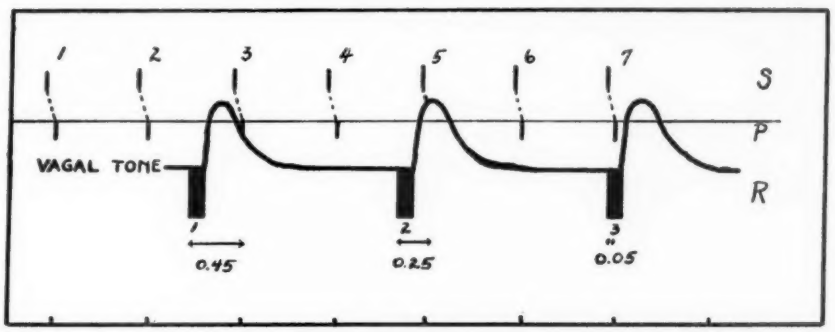

Fig. 2.—Diagram illustrating the relationship of idioventricular contractions to alterations in vagal tone and the occurrence of S-A block. Uppermost row of vertical lines indicates sinus impulse (*S*). The oblique dotted lines represent sinoauricular conduction (exaggerated for clarity). These end in vertical lines denoting auricular contraction (*P*), except at 5. R_1, R_2 and R_3 represent QRS complexes upon which there is a curve depicting the change in vagal tone after each idioventricular beat. Note that this curve does not rise until the end of the QRS complex (0.11 sec. See text). The horizontal line above *P* represents the threshold of vagal tone above which S-A block occurs (duration, 0.26 sec.). When R-P is 0.45 sec., S-A block does not occur because vagal tone has just fallen below threshold. When R-P is 0.25 sec., S-A block does occur because vagal tone is at its height. An R-P of 0.05 sec. results in an elevated vagal tone just after the normal sinus impulse, and therefore no S-A block occurs. P-P = 0.80 sec. R-R = 1.80 sec.

coincided with the time of increased vagal tone. And so it did. The latent period between the beginning of the electrical effects of ventricular systole and the mechanical effect upon the aortic and sinus nerves is 0.11 sec., according to Ashman and Gouaux.[19] Another 0.01 sec. is required for the reflex arc to be completed. Therefore, 0.12 sec. after the initial deflection of the QRS complex one can expect a depression of the excitability of the sinoauricular tissue. In our case this effect was apparently sufficient to cause sinoauricular block whenever the R-P distance was between 0.13 sec. and 0.39 sec. When the R-P interval exceeded 0.42 sec., block never occurred, probably because by this time the vagal tension had subsided and was no longer sufficient to interfere with sinoauricular conductivity. Similarly, an R-P interval of less than 0.11 sec. was too short to produce a heightened vagal tone at the time of the normal sinus impulse. These facts are depicted graphically in Fig. 2.

Tracings taken Dec. 16 and 28, 1939, showed that after each idioventricular contraction there was also a slowing of the auricular rate, in addition to the specialized occurrence of sinoauricular block. This would indicate that the increase in vagal tone had both a chronotropic and dromotropic effect. On one occasion $\frac{1}{75}$ grain of atropine sulfate was given hypodermically with no effect on the auricular rate or the sinoauricular block.

ANALYSIS OF OUR DATA ON RETROGRADE CONDUCTION

Inverted P waves after certain idioventricular contractions, representing retrograde auricular contractions, occurred in tracings taken on four different days. These were best seen in the Leads II and III. Fig. 1 illustrates this condition. P^1 designates the retrograde auricular contraction. The following observations are noteworthy:

1. The P-P interval varied between 0.71 and 0.90 sec. in all of our tracings.

2. The retrograde P waves appeared only in part of the second half of diastole of the auricles, namely, only where the preceding P-R interval was 0.40 to 0.76 sec. (Table II).

TABLE II

RELATIONSHIP OF THE PRECEDING P-R INTERVAL TO THE FREQUENCY OF OCCURRENCE OF RETROGRADE CONDUCTION

P-R (SEC.)		0.00-0.39	0.40-0.47	0.48-0.71	0.72-0.76	0.77-0.88
Retrograde conduction	Present (no.)	0	7	46	6	0
	Absent (no.)	62	8	0	5	4

3. The $R\text{-}P^1$ interval varied between 0.14 sec. and 0.20 sec. and was roughly inversely proportional to the length of the preceding P-R interval (Fig. 3).

4. The sum of $P\text{-}P^1$ and $P^1\text{-}P$ was equal to twice the usual P-P interval, and the $P^1\text{-}P$ distance exceeded the usual P-P interval by 0.02-0.28 sec. Therefore, there was a compensatory pause of the auricles.

The normal sinus rhythm in our case was not disturbed by the premature retrograde contraction of the auricles. This would be possible only if there were an auriculosinus block.[21] There was also sinoauricular block as a result of refractoriness of the auricle after the retrograde systole. Therefore, on these days there were both "entrance" and "exit" blocks around the sinoauricular node.

There are two possible mechanisms for the production of retrograde auricular contraction in a case of complete heart block. The first is mechanical stimulation of the irritable auricle[13] or A-V node[14, 16] by the impact of ventricular systole. The second is retrograde conduction of the impulse from the ventricle via intact conduction fibers within the scar, as suggested by Danielopolu and Danulesco[15] and Wolferth and McMillan.[17] In the present state of our knowledge, it can be said

that mechanical stimulation of the auricles is probably not the underlying cause. We feel that the more likely mechanism is either mechanical stimulation of the bundle of His or A-V node above the scar, or actual retrograde conduction through the area of block in the bundle of His. In our case it seems that the premature auricular contraction received its impulse from a focus in the conduction tissue, because (1) it always occurred late in the interauricular interval after the refractory period of the A-V tissue, (2) the P waves were always of the same contour, and (3) the R-P[1] interval varied directly with the duration of the recovery phase of the tissue, as measured by the preceding P-R interval.

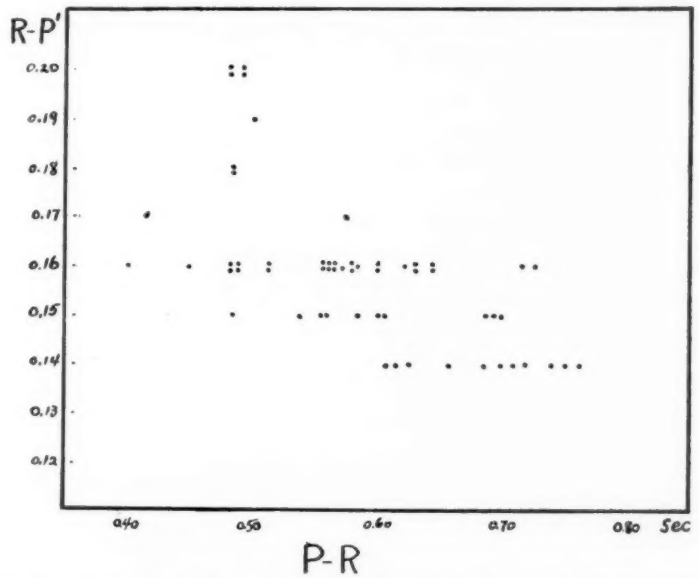

Fig. 3.—Scatter graph showing the inverse relationship between the retrograde conduction time (R-P[1]) and the length of the preceding P-R interval or recovery phase. This type of correlation resembles that seen with progressive recovery. On the other hand, in the supernormal phase of excitability, conduction time is shortest early, and longest late, in the recovery period.

The retrograde conduction appeared only when the P-R interval varied from 0.40 to 0.76 sec. These limits coincide closely with those reported by others as representing the supernormal phase. Kline, et al.,[18a] found it to be 0.32 to 0.65 sec. In cases of paroxysmal complete heart block, normal auriculoventricular conduction occurred when the Q-P interval was 0.425 to 0.708 sec.,[22] 0.31 to 0.795 sec.,[23] and 0.45 to 0.74 sec.[24] Nahum and Hoff[25] have ascertained the supernormal phase of the ventricular musculature of cats, dogs, and monkeys and found it to extend approximately from 0.40 to 0.64 sec. after the onset of the QRS complex. These limits correspond closely to those for the conduction tissue. However, the recovery curve of the conduction tissue in our case showed improving excitability with increasing recovery

(Fig. 3). This type of curve, with a late plateau, resembles the curve of progressive recovery, rather than that previously reported as being characteristic of a supernormal phase. Such curves, constructed from similar observations on man by Lewis and Master[22] and Ashman and Herrmann,[23] and also on bloodless turtle hearts,[23] show a rapid rise with an early peak, and then a gradual fall. Although our observations do not exclude the influence of a supernormal phase of the conductive system in the production of retrograde conduction, in our case we feel that progressive recovery of the conduction tissue adequately explains this phenomenon. The absence of retrograde conduction when P-R was above 0.76 sec. does not speak in favor of the importance of the supernormal phase in retrograde conduction but is sufficiently explained by the fact that a retrograde stimulus which came at this time reached the auricle too late to prevent an orthograde auricular contraction.

DISCUSSION

In our opinion, sinoauricular block is never a physiologic phenomenon. It is always due to more than one factor. In our case it was caused by a combination of myocardial fibrosis in the region of the sinoauricular node, increased vagal tension, and myocardial malnutrition secondary to coronary insufficiency. There was no relationship between digitalis and sinoauricular block or retrograde auricular conduction.

SUMMARY

1. A case of complete heart block with occasional sinoauricular block and retrograde auricular beats is presented.

2. The dropping of P waves occurred in a definite relation to the beginning of the preceding idioventricular contraction. The time of the sinoauricular block coincided with the time of the highest vagal tone after the idioventricular beats.

3. Retrograde P waves occurred only when the preceding P-R interval was 0.40 to 0.76 sec. Although that coincided with the supernormal phase in the auriculoventricular node or bundle of His above the scar, this phase probably played no important role in the retrograde conduction in our case.

4. The time of the retrograde conduction in our case bore a definite relation to the length of the preceding P-R interval. This may be expected to occur when the conduction tissue is damaged and the rate of conduction varies with the degree of its recovery.

REFERENCES

1. Levine, S. A.: Observations on S-A Block, Arch. Int. Med. **17**: 153, 1916.
2. Smith, S. C.: The Heart Irregularity Called "Sino-Auricular Block," Am. J. M. Sc. **162**: 575, 1921.
3. White, P. D.: Clinical Observations on Unusual Mechanisms of the Auricular Pacemaker, Arch. Int. Med. **25**: 420, 1920.

4. Lewis, T.: The Mechanism and Graphic Registration of the Heart Beat, London, 1925, Shaw & Sons, Ltd.
5. Wallace, A. W., and Katz, L. N.: Sino-Auricular Block, Am. Heart J. 6: 478, 1930.
6. Spuhler, O.: Aspects of S-A and Interauricular Conduction Disturbances, Cardiologia 3: 244, 1939.
7. Mackenzie, J.: The Cause of Heart Irregularity in Influenza, Brit. M. J. 2: 1411, 1902.
8. Wenckebach, K. F.: Die Unregelmässige Herztätigkeit, Leipzig, 1914, W. Englemann.
9. Barlow, P.: The Clinical Occurrence of S-A Block, Lancet 212: 65, 1927.
10. Zárday, I.: Unusual Features of Two Cases of S-A Block, Am. Heart J. 12: 339, 1936.
11. Feldman, L.: S-A Block and Ventricular Escapes in Case of Syphilitic Heart Disease With Bundle Branch Block; Vagus Overactivity on Sinus Node Demonstrated, M. Clin. North America 18: 1383, 1935.
12. Van Buchem, F. S. P.: Explanation of S-A and A-V Block, Acta Med. Scandinav. 95: 16, 1938.
13. Cohn, A. E., and Fraser, F. R.: The Occurrence of Auricular Contractions in a Case of Incomplete and Complete Heart Block Due to Stimuli Received From the Contracting Ventricles, Heart 5: 141, 1914.
14. Wilson, F. N., and Robinson, G. C.: Two Cases of Complete Heart Block Showing Unusual Features, Arch. Int. Med. 21: 166, 1918.
15. Danielopolu, D., and Danulesco, V.: Sur le conductibilité retrograde et sur la phase refractaire de l'oreillette, Arch. d. mal. du coeur 15: 365, 1922.
16. Barker, P. S.: Occurrence of Auricular Beats Due to Stimulation of Auricles by Contracting Ventricles During Complete Heart Block, Am. Heart J. 1: 349, 1926.
17. Wolferth, C. C., and McMillan, T. M.: Observation on Mechanism of Relatively Short Intervals in Auriculoventricular and Ventriculoauricular Sequential Beats During High Grade Heart Block, Am. Heart J. 4: 521, 1929.
18. (a) Kline, E. M., Conn, J. W., and Rosenblum, F. F.: Variations in A-V and V-A Conduction Dependent Upon the Time Relations of Auricular and Ventricular Systole: The Supernormal Phase, Am. Heart J. 17: 524, 1939.
(b) Kisch, Bruno, and Sakai, S.: Die Änderung der Function der extracardialen Herznerven, Arch. ges. Physiol. 198: 65, 1923.
19. Ashman, R., and Gouaux, J. L.: Reflex Inhibition of Human Heart: Complete A-V Block and Parasystole, Proc. Soc. Exper. Biol. & Med. 37: 25, 1937.
20. Kisch, Bruno: Beobachtungen bei einem Kranken mit totalen Block, Cardiologia 2: 47, 1938.
21. Kisch, Bruno: Das Vorkommen und der Nachweis von interpolierten Vorhofextrasystolen, Ztschr. f. d. ges. exper. Med. 25: 188, 1921.
22. Lewis, T., and Master, A. M.: Supernormal Recovery Phase Illustrated by Two Clinical Cases of Heart-Block, Heart 1: 371, 1924.
23. Ashman, R., and Herrmann, G. R.: Supernormal Phase in Conduction and Recovery Curve for Human Junctional Tissues, Am. Heart J. 1: 594, 1926.
24. Wolferth, C. C.: So-Called Supernormal Phase in the Human Heart, Am. Heart J. 3: 703, 1928.
25. Nahum, L. H., and Hoff, H. E.: Interpretation of U Wave of the Electrocardiogram, Am. Heart J. 17: 585, 1939.

Department of Reviews and Abstracts

Selected Abstracts

Herrick, J. F., Corcoran, A. C., and Essex, H. E.: The Effects of Renin and of Angiotonin on the Renal Blood Flow and Blood Pressure of the Dog. Am. J. Physiol. **135**: 88, 1941.

Both renin and angiotonin decrease the blood flow in the renal artery and increase arterial pressure. In a few observations on the flow in the femoral artery it was found that both renin and angiotonin caused a diphasic effect consisting of an initial transient decrease followed by a somewhat more pronounced and prolonged increase. Pentobarbital sodium anesthesia did not seem to alter the hemodynamic effects of these substances.

AUTHORS.

Page, I. H., McSwain, B., Knapp, G. M., and Andrus, W. D.: The Origin of Renin-Activator. Am. J. Physiol. **135**: 214, 1941.

The liver is the chief source of renin-activator, and its removal or damage by toxic substances in normal and hypertensive dogs reduces the renin-activator content of plasma and hence the pressor response to injected renin. The pressor response to angiotonin and the angiotonin-activator of blood remains unaffected by these procedures.

AUTHORS.

Rodbard, S.: The Effect of Nephrectomy on the Blood Pressure Response to Renin and Angiotonin. Am. J. Physiol. **135**: 124, 1941.

The intensity and duration of the blood pressure response to renin is essentially the same before and after nephrectomy. In some animals, however, the duration of the response is somewhat increased following nephrectomy.

Renin has many properties which would suggest that it is closely related to the mechanism responsible for arterial hypertension of renal origin. Among these are the consistent presence of renin in kidney extracts, the reaction of renin with some of the constituents of the blood (renin-activator) to produce a new pressor material (angiotonin), and the reduction in intensity of response to renin seen in adrenalectomized animals. Nevertheless it appears that renin has not fulfilled one of the criteria necessary for the substance responsible for hypertension, since no consistent potentiation of the intensity or duration of the blood pressure response occurs after nephrectomy. The increase in duration of the response seen in some animals after nephrectomy is not of the magnitude predicted for the mediator of hypertension by our previous experiments.

The similarity in the blood pressure response to angiotonin before and after total nephrectomy suggests that the kidney is not responsible for the destruction or elimination of this substance.

AUTHOR.

Levy, R. L., Patterson, J. E., Clark, T. W., and Bruenn, H. G.: "Anoxemia Test." J. A. M. A. **117**: 2113, 1941.

This study is based on 373 anoxemia tests performed on 137 persons during the past thirty-nine months. On all but seventeen patients the test was done at least twice; on some it was done as often as twenty times.

A positive reaction was not observed in any patient without cardiac disease or severe anemia.

A positive reaction may be regarded as a sign of coronary insufficiency; a negative reaction does not exclude disease of the coronary arteries.

The occurrence of pain during a test with a negative result, particularly if it appears during the first ten minutes of induced anoxemia, affords presumptive evidence of a diminished coronary reserve. Under these circumstances the patient should be observed carefully for further signs of coronary disease and managed conservatively.

The test is simple and safe. In the past four years it has been done 1,024 times on 442 persons. Unpleasant reactions have been observed forty-six times in thirty-six patients. But there have been no serious effects, and the course of the disease has not been affected unfavorably as the result of repeated tests.

The test is helpful in the differential diagnosis of conditions producing pain in the chest. When the reaction is positive, it serves to distinguish discomfort due to coronary insufficiency from that caused by other disorders. It is useful in following variations in the coronary reserve and therefore in appraising the efficiency of the coronary circulation at the time of its performance. Serial observations reflect, in a general way, the trend of the clinical course. The test does not furnish evidence which makes it possible to predict the future occurrence of coronary occlusion. It affords an index of the adequacy of the coronary blood flow within the undefined limits, but it yields no information as to the nature or extent of the pathologic lesions in the heart.

AUTHORS.

Parkinson, J., Papp, C., and Evans, W.: The Electrocardiogram of the Stokes-Adams Attack. Brit. Heart J. **3**: 171, 1941.

Stokes-Adams disease is a name applicable to patients with heart block who suffer from recurrent attacks of loss of consciousness due to ventricular standstill, ventricular tachycardia, ventricular fibrillation, or a combination of these. During a Stokes-Adams attack from ventricular standstill the auricle continues to beat, whereas in cardiac syncope of other types there is, as a rule, total cardiac standstill. Cardiac syncope of neurogenic origin (e.g., ordinary fainting and ventricular standstill from disease affecting the vagus or carotid sinus) and cardiac syncope of myocardial origin without heart block (e.g., in nodal bradycardia and in paroxysmal ventricular tachycardia) are excluded by this definition, although there are borderline cases.

The cardiac mechanism of Stokes-Adams attacks was studied on electrocardiograms recorded during the period of unconsciousness in eight cases and in fifty-six reported cases. These fall into four groups or types and are tabulated according to the electrocardiographic basis of the attack. Group I (twenty-eight cases and five of this series) includes those with ventricular standstill alone. Group II (sixteen reported cases and two of this series) includes those with (a) low ventricular tachycardia and (b) high ventricular tachycardia and fibrillation, when either is followed by ventricular standstill. Group III (twelve reported cases and one of this series) includes those with high ventricular tachycardia and fibrillation without ventricular standstill. Group IV includes those rare cases with extreme bradycardia in heart block.

It is evident that ventricular standstill alone is not the only cardiac lapse that determines a Stokes-Adams attack. It is often due to ill action and not to inaction of the ventricle. Ventricular standstill is responsible for about 55 per cent; ventricular tachycardia (with or without ventricular fibrillation), followed by ventricular standstill, for 25 per cent; and ventricular tachycardia without ventricular standstill, for 20 per cent.

Ventricular standstill is sometimes consecutive to a rise in the auricular rate. As exertion or emotion so seldom determines ventricular standstill, this increase in the auricular rate probably originates locally in the auricle and not from any nervous influence.

During a short ventricular standstill (below twenty seconds), the auricle beats regularly, often at an increasing rate, and the persistence of P waves during the ventricular standstill is a feature distinguishing it from total standstill of cardiac syncope. During a long ventricular standstill (above twenty seconds), or when ventricular standstill is preceded by high ventricular tachycardia and fibrillation (Group II), the auricle may show slower, irregular, and ectopic P waves, auricular fibrillation and flutter, or it may even stop.

In a group with ventricular tachycardia, multiple and variable extrasystoles and varying bundle branch block complexes between the attacks are common, as might be expected. Low ventricular tachycardia (up to 160) does not produce unconsciousness, but it provokes the subsequent ventricular standstill that does produce it (Group IIa). High ventricular tachycardia and fibrillation (200-500) produce unconsciousness (Group III), and this may be prolonged by the subsequent ventricular standstill (Group IIb). The electrocardiogram of ventricular tachycardia is composed of regular deflections like bundle branch block, which at high rates merge into simple undulations; yet the term "ventricular flutter" need not be used, for the resemblance to auricular flutter is superficial.

Ventricular fibrillation is distinguished from ventricular tachycardia by its irregularity in both rate and form, although the rate per minute may be the same, higher, or even lower. High ventricular tachycardia easily passes into fibrillation, which ends with ventricular standstill or with gradual resumption of the basic rhythm through a period of low ventricular tachycardia or of varying extrasystolic complexes.

The essential basis of an attack can be decided only by an electrocardiogram. The prolongation of unconsciousness or its late onset in ventricular tachycardia and fibrillation cannot distinguish this group from that of ventricular standstill alone, because other factors may influence unconsciousness, e.g., the suddenness of the development of block or of the fall in rate, a rapid succession of attacks, and the state of the cerebral arteries. For similar reasons it is difficult to state exactly what must be the duration of the circulatory arrest to produce syncope or convulsions.

In established complete heart block or in partial heart block the Stokes-Adams attack may belong to any group, whereas in paroxysmal heart block it is generally in Group I, i.e., ventricular standstill alone. After coronary thrombosis, attacks due to ventricular standstill alone may occur, as well as those due to ventricular tachycardia and fibrillation.

No prognostic significance can be attached to the grade of heart block, partial or complete, obtaining between the attacks, but the electrocardiographic nature of the attack has great significance in prognosis—and doubtless in treatment, although this is not considered here. Patients with ventricular standstill (Group I) have a fair chance of recovery and often survive for many years, whereas those with ventricular tachycardia and fibrillation (Groups II and III) seldom recover and then rarely survive for more than a year.

AUTHORS.

LeRoy, G. V., and Snider, S. S.: The Sudden Death of Patients With Few Symptoms of Heart Disease. J. A. M. A. 117: 2019, 1941.

The myocardial infarct responsible for sudden death need not be so large that muscular failure alone is responsible.

Myocardial infarction may occur without complete closure of a coronary artery and without the classic syndrome of pain, shock, and collapse.

A myocardial infarct usually causes some symptoms, even though they may be mild.

The sudden death of a patient with infarction of the myocardium is due to a reflex coronary vasoconstriction whose stimulus is the infarct, whose afferent pathway is the cardiosensory innervation, and whose efferent pathway is the vagus. The result of this reflex vasoconstriction in a susceptible person is fatal ventricular fibrillation.

The probability of the establishment of this lethal reflex may be decreased by the use of certain drugs (atropine and the xanthine derivatives), by cardiosensory denervation, and reasonably, but to a lesser extent, by simple rest in bed.

AUTHORS.

Cooke, W. T., and White, P. D.: Tricuspid Stenosis, With Particular Reference to Diagnosis and Prognosis. Brit. Heart J. 3: 147, 1941.

Between 1920 and 1937, 217 cases of rheumatic heart disease were observed in 4,300 autopsies at the Massachusetts General Hospital. In forty-seven of these, the tricuspid valve was affected, but in only thirty was tricuspid stenosis believed to be of sufficient degree to be of clinical significance.

In addition, twelve cases of tricuspid valve stenosis have been examined clinically by the authors during the past three years, including three cases that came to autopsy.

There were twenty-one males and twenty-one females in the combined groups of thirty-three autopsied and nine clinical cases.

The age at death varied between 10 and 59 years in the thirty cases with autopsies, and the average was 23 years. The average age at death in 160 cases of rheumatic heart disease in the same hospital was 42 years.

The cases of tricuspid valve disease may be divided into two groups: a young group in the first three decades dying of rheumatic fever, and an older group in whom the mechanical factors induced by the lesions played an increasingly important part.

The symptoms in the younger group were almost indistinguishable from those of rheumatic fever. The older group was characterized by the relatively long survival after the appearance of congestive symptoms and signs indicative, in most other circulatory disorders, of death in the near future.

The diagnosis of tricuspid disease in the young group indicates serious involvement of the myocardium and a poor prognosis. In the older group, owing to the "safety valve" function of the tricuspid valve, the patients may live many years providing there is no recurrence of severe rheumatic fever.

The diagnosis of tricuspid disease is difficult, but, when due attention is paid to the history, clinical examination of the patient, and x-ray examination of the heart, the diagnosis should be made more frequently. No one sign is pathognomonic, but in the order of importance the clues may be listed as follows (their chief value lies in combination): a mid-diastolic murmur localized over the tricuspid area, chronic and well-marked systolic pulsation of the deep jugular veins, ascites in the absence of lung congestion, enlargement of the heart shadow to the right, deviation of

the esophagus to the left, cyanosis and sometimes jaundice, enlarged liver with or without pulsation, persistently raised venous pressure, and prolonged right heart circulation time. The chief reason that the diagnosis is not made more often is that the physician does not look for these clues and signs.

The diagnosis of tricuspid disease is important as an aid in the more accurate determination of prognosis and treatment.

AUTHORS.

Martin, A. T.: Twenty Years' Observation of 1,438 Children With Rheumatic Heart Disease. J. A. M. A. 117: 1663, 1941.

A true evaluation of the results of convalescent care for children with rheumatic heart disease is not possible without a comparable control group of children kept in their home environment. Such a group of children was not available or possible for this study. The validity of any conclusions depends upon this.

Mortality figures were related closely to the severity of cardiac damage and were higher in the polycyclic types of rheumatic infection.

Future planning for children with rheumatic heart disease should provide prolonged bed rest and medical supervision, preferably in a sanatorium or foster home. This should follow care in the hospital. More beds should be provided for this purpose.

Convalescent care should be provided for a carefully selected group of children after the rheumatic infection has become quiescent and should be carried on for at least six months. Optimum benefit has been observed in the monocyclic group with minimal cardiac injury.

In the convalescent care of the cardiac child, attention to the psyche is quite as important as attention to the soma. The two should be integrated. The educational program and occupational therapy are important adjuncts in the process of rehabilitation.

The role of the trained social worker and adequate nursing supervision are important in the home when the child returns from the convalescent home or sanatorium.

AUTHOR.

Clawson, B. J.: Relation of the "Anitschkow Myocyte" to Rheumatic Inflammation. Arch. Path. 32: 760, 1941.

The "Anitschkow myocyte," the myocardial reticulocyte (Ehrlich and Lapan) or the cardiac histiocyte, is normally found in the heart and heart valves.

It responds in flammation by an increase in cytoplasm and is often the chief cell to respond in rheumatic inflammation and in experimental inflammation in the heart.

It is not a characteristic cellular response in rheumatic inflammation, for it is not found in rheumatic subcutaneous nodules.

AUTHOR.

Stowell, D. D., and Button, W. H., Jr.: Observations of the Prophylactic Use of Sulfanilamide on Rheumatic Patients. J. A. M. A. 117: 2164, 1941.

Sulfanilamide can be a lethal drug when used prophylactically on the rheumatic patient.

At the present state of knowledge the drug should not be used in ambulatory rheumatic children and adolescents.

AUTHORS.

Goldring, W., Chasis, H., Ranges, H. A., and Smith, H. W.: Effective Renal Blood Flow in Subjects With Essential Hypertension. J. Clin. Investigation 20: 637, 1941.

The filtration rate (C_{in}), diodrast clearance (C_d) and the maximal rate of tubular excretion of diodrast (T_{md}) have been examined in sixty subjects with essential hypertension. Comparison of the data with those previously reported for the normal kidney reveals the following facts.

An extreme reduction in T_{md} occurs in advanced states of the disease, and for the entire series of sixty subjects T_{md} is below or in the lower range; these facts lead us to infer that the disease is characterized by a progressive impairment of tubular function which proceeds at varying pace in different subjects.

In some patients impairment of tubular function appears to outrun impairment of glomerular function (formation of impotent tubules), so that the filtration rate remains within the limits of normal variation when T_{md} has been substantially reduced. In the nature of the renal circulation, elevation of the mean systemic blood pressure or the formation of impotent tubules may increase the quantity of diodrast-containing blood perfusing the residual functional tissue. We believe that in either case the anomalous condition will be revealed by the presence of a high filtration rate per unit of functional tubular tissue.

Deleting such anomalous instances, the effective blood flow per unit of functional tubular tissue, or the ratio C_d/T_{md}, in the remaining subjects, ranges downward from the mean normal to highly subnormal values, indicating relative renal ischemia. Since this ischemia is associated with an elevation of the filtration fraction, it is attributed to increased tone of the efferent glomerular arterioles. On the available evidence, this increased efferent tone may in turn be attributed to the presence of one or more pressor substances in the blood. The increased efferent tone is functionally reversible, in that renal hyperemia, associated with a fall in filtration fraction (efferent dilatation), follows the administration of suitable doses of pyrogen, as in normal subjects. The absolute values of C_d/T_{md} in hypertensive subjects during hyperemia are of the same order of magnitude as in normals during the hyperemic reaction.

In most hypertensive subjects, T_{md} has been reasonably constant over a considerable period and has not increased during pyrogenic hyperemia. In some subjects, however, T_{md} was increased during hyperemia, indicating that in these and perhaps in other subjects substantial quantities of tubular tissue may be ischemic under basal conditions. Spontaneous changes in T_{md} have been observed which may reflect changes in the quantity of tubular tissue available to perfusion or trophic changes in the excretory tissue itself.

In brief, the functional picture presented by the hypertensive kidney is consonant with the theory that there is present in the blood in hypertensive disease one or more pressor substances which produce a reversible renal ischemia by constriction of the efferent glomerular arterioles. In addition, there is profound impairment and ultimate destruction of tubular function. Which of these precedes the other is as yet undetermined.

There is no evidence in the present investigation to warrant the conclusion that renal ischemia is the primary cause of essential hypertension. The renal ischemia demonstrated here, which has its origin in increased tone of the efferent glomerular arterioles, appears to be one of the sequelae of the hypertensive process. We may place on record our belief that primary renal ischemia in man can, under proper quantitative circumstances, initiate a hypertensive process, but whether or not the secondary ischemia, associated with efferent hypertonus, which is present in hypertensive subjects generally, contributes to the progress of the disease cannot be

answered from this study. Alternatively, the possibility cannot yet be excluded that the appearance of pressor and cytotoxic substances in the blood follows a metabolic disorder in the kidney or in other organs and is wholly independent of renal ischemia.

AUTHORS.

Chasis, H., and Redish, J.: Effective Renal Blood Flow in the Separate Kidneys of Subjects With Essential Hypertension. J. Clin. Investigation **20**: 655, 1941.

The clearance method has been applied to the measurement of the renal blood flow, the filtration rate, and the tubular excretory mass in the separate kidneys of patients with essential hypertension. The results of these observations indicate that the destruction of tubular tissue progresses equally on the two sides in hypertensive disease and that the functional disturbance in respect to blood flow and filtration rate is shared equally by the two kidneys.

In no instance in the twenty-one hypertensive subjects picked at random is there any indication of a unilateral ischemic kidney. If it is predicated that renal ischemia is the primary causal factor in all essential hypertension, it would be expected that unilateral impairment of renal function would be observed more frequently than bilateral impairment. The absence of unilateral impairment in these subjects argues against the above premise.

AUTHORS.

Page, I. H.: The Pressor Response of Normal and Hypertensive Dogs to Renin and Angiotonin. Am. J. Physiol. **134**: 789, 1941.

Inconclusive evidence suggests that the blood vessels of hypertensive animals and man are abnormally sensitive to pressor agents; hence no more than normal amounts of them in the blood would be required to cause hypertension. It is, therefore, of importance to learn whether this is true of such substances as renin and angiotonin because of the belief that they may be involved in the genesis of chronic arterial hypertension. It is this problem with which this investigation is concerned.

Induction of experimental renal hypertension in dogs does not increase the pressor response to angiotonin. On the other hand, in such animals renin causes somewhat greater responses. The increased response to renin appears to be due to greater formation of angiotonin from combination of renin and renin-activator and is not the result of increased sensitivity of the vascular system of hypertensive animals.

AUTHOR.

Coffen, T. H., Rush, H. P., and Miller, R. F.: Traumatic Complete Heart Block of Eighteen Years' Duration. Northwest Med. **40**: 195, 1941.

In this case it is believed that injury from a fall was followed by a lesion in the conducting pathway, resulting in auriculoventricular dissociation found seven years later when the patient was 10 years old. There have been no changes in the electrocardiograms in the last ten years. He has grown and developed normally and is following normal physical activities.

This case is reported because it is the only one in which auriculoventricular block from injury occurred in childhood that we have been able to find. There are only five other cases in which auriculoventricular block resulted from nonpenetrating injury. It has persisted for eighteen years in our patient. There have been no evidences of heart failure or Stokes-Adams syndrome.

AUTHORS.

Atlas, Lawrence N.: Traumatic Vasospastic Dystrophy of the Extremities. Arch. Surg. 42: 1042, 1941.

Trauma to an extremity with injury to a blood vessel or its nerve supply may result in a syndrome which the author calls traumatic vasospastic dystrophy. As a result of trauma to a blood vessel, without ischemia, there may occur pain, subjective and objective coldness, hyperhidrosis, cyanosis, tense, shiny skin, firm, tender edema, muscular weakness, joint fixation, and decalcification of bone. Three patients with this syndrome are presented. Theories as to the cause of the clinical picture are discussed.

NAIDE.

Roome, N. W.: Sympathetic Blockade in Peripheral Vascular Accidents. Canad. M. A. J. 44: 594, 1941.

Blockade of the lumbar sympathetic chain, by infiltration with procain solution, was found to give prompt and complete relief of otherwise intractable pain in two cases of embolism of the lower extremities.

The method is recommended for trial in cases of embolism, either alone or in combination with embolectomy, and should also be considered in the management of wounds of the major arteries, and of arterial thrombosis and acute thrombophlebitis.

AUTHOR.

Master, A. M.: Roentgenoscopy as a Diagnostic Aid in Coronary Occlusion. Am. J. Roentgenol. 45: 350, 1941.

Roentgenoscopic observations of ventricular contraction in 300 private patients are recorded. More than half of these had coronary occlusion; the remainder included other types of heart disease and normal subjects.

The technique employed is described in detail. Roentgenoscopy is shown to be a simple and inexpensive method of diagnosing coronary occlusion with myocardial infarction

Abnormalities in pulsation were present in 75 per cent of the cases of coronary occlusion. Systolic expansion (reversal of pulsation) of the left ventricle, observed in 50 per cent of these cases, is characteristic, if not pathognomonic, of myocardial infarction. "Lag" and "doubling" of pulsation are incomplete forms of systolic expansion. Systolic expansion is seen in practically every case of large heart with ventricular aneurysm. Absence and diminution of pulsation were present in 25 per cent of cases with coronary occlusion, but also occurred in other types of heart disease.

The abnormal pulsations observed were located in the apical and the supra-apical portions of the left ventricle in almost 85 per cent of the cases studied.

The evidence of abnormal contraction did not depend upon the location of the infarct as determined electrocardiographically.

The incidence of abnormal pulsation in coronary occlusion was found to be greater when the heart was enlarged. When the area of abnormal pulsation was large, the prognosis was poor.

Systolic expansion may appear directly after the coronary occlusion and persist for many years. Its disappearance, or a change to absence or diminution of pulsation, is of favorable significance.

In normal hearts the pulsations are always normal. Hypertension alone does not produce changes. Disease of the coronary artery, without occlusion, did not exhibit systolic expansion or absence of pulsation. When these conditions are

present, coronary occlusion should be suspected. Systolic expansion is seen occasionally in cases of aortic insufficiency with cardiac enlargement.

Roentgenoscopy should form part of the routine examination of every cardiac suspect. It may be positive when the physical examination and electrocardiogram are negative.

AUTHOR.

Sheehan, D., Mulholland, J. H., and Shafiroff, B.: Surgical Anatomy of the Carotid Sinus Nerve. Anat. Rec. **80**: 431, 1941.

The common variations of the carotid sinus nerve and of the innervation of the carotid body have been described, based on thirty-three special dissections of this region.

The carotid sinus is innervated by the glossopharyngeal, vagus and cervical sympathetic, and exceptionally by the hypoglossal. The fibers reach the sinus in two ways, (1) along the carotid sinus nerve and (2) through an intercarotid plexus and the carotid body.

The anatomy suggests the feasibility of dividing the carotid sinus nerve in preference to extensive stripping of the carotid artery, in the surgical treatment of carotid sinus syncope.

AUTHORS.

Hyman, A., and Leiter, H. E.: Surgery of the Inferior Vena Cava in Urologic Conditions. J. Urol. **45**: 813, 1941.

A series of eleven surgical procedures on the vena cava is reported. Experimental and surgical procedures demonstrate that complete ligation of the cava below the renal veins is compatible with life. In this series the vena cava was accidentally injured in four instances, whereas in the other seven cases the surgery was deliberate. It may be stated that the deliberate type of surgery on the cava is generally associated with renal neoplasms or adherent pyonephrotic kidneys. With the newer sulfanilamide preparations in general use, the indications for surgery on the cava in inflammatory conditions will be reduced to a minimum. In these eleven cases there were three postoperative deaths. As stressed in this paper, the renal vein and vena cava should always be explored in right renal neoplasms. For this reason, a wide exposure, necessitating resection of one or two ribs, is advisable. In some of the cases reported patients have survived a three-year period where thrombi have been removed from the vena cava. The presence of a vena cava tumor thrombus, while certainly grave, does not necessarily imply an immediate fatal course.

AUTHORS.

Pratt, G. H., and Wright I. S.: The Surgical Treatment of Chronic Lymphedema (Elephantiasis). Surg., Gynec. & Obst. **72**: 244, 1941.

A surgical procedure is described for the treatment of chronic lymphedema. The importance of proper preoperative preparation is stressed. About three-fourths of the circumference of the superficial and deep fascia are excised en masse. A broad-based pedicle tube graft is employed where it is necessary to remove devitalized skin. In addition to skin replacement, the pedicled graft drains the skin lymphatics and thus supplies a new method of aiding skin lymphatic drainage.

NAIDE.

Friedbacher, K.: Experimental Collateral Circulation of the Heart. Surg., Gynec. & Obst. **72**: 1003, 1941.

The author's experiments tend to show the following conclusions.

The direct anastomosis of internal mammary artery to the coronary might be possible.

The omental graft lends itself best as a possible source of extracardiac blood supply to the myocardium. The graft remains pliable, and the heart action is free.

Muscle grafts become quite firm and interfere with heart action; a layer of fibrosis develops between skeletal and myocardial muscles.

The heart of the healthy dog withstands diminution of its normal blood supply until it reaches the point of infarction and then recovers as demonstrated by the electrocardiogram.

Vascular connections between the graft and the heart muscle can be demonstrated in microscopic dissections.

Additional experiments are being carried out at the present time to prove further these contentions.

AUTHOR.

Cole, W. H., Weber, R. D., and Keeton, R. W.: Pericardiectomy for Chronic Constrictive Pericarditis. Surg., Gynec. & Obst. **72**: 1008, 1941.

Undoubtedly, innumerable cases of constrictive pericarditis are erroneously diagnosed as congestive heart failure, hepatic cirrhosis, etc., because of the similarity of symptoms to those of constrictive pericarditis. It is particularly important that this error be avoided because sufficient operative reports are now available to establish the fact that, although the mortality rate is high, the results otherwise are excellent. Perhaps the first symptom of constrictive pericarditis is weakness, followed soon by dyspnea upon exertion. Of great diagnostic significance is the fact that in this disease the dyspnea is not present while the patient is inactive and that ascites precedes edema of the extremities. Distended neck veins, high venous pressure, paradoxical pulse, and small cardiac shadow constitute important evidence for the diagnosis.

Since conservative treatment of the disease is hopeless, operation should be performed early, before myocardial damage due to compression, etc., is irreparable. Results are much better in young people; very few patients in adult life survive the operation. Results may not be immediate, as emphasized by the fact that in one of our patients strength was still subnormal one year following operation, but two years after operation he felt perfectly normal and was working daily running a press.

AUTHORS.

Bigger, I. A.: Peripheral Vascular Injuries. Ann. Surg. **113**: 677, 1941.

The treatment of injuries to the major peripheral vessels forms an important part of modern war surgery. In the past, even during the World War I, vascular suture was not often feasible. Since we now have more effective means of preventing thrombosis at the line of suture, and of combating infection, suture should play a more important role in reducing peripheral gangrene due to vascular injuries.

When important arteries are occluded, certain measures should be employed to combat ischemia, among them ligation of the concomitant vein or veins and, if there

is any evidence of insufficient collateral circulation, sympathetic nerve block. In addition to these local measures, certain general measures, of which the most important is blood replacement, must also be given consideration.

NAIDE.

Homans, John: Minor Causalgia Following Injuries and Wounds. Ann. Surg. **113:** 932, 1941.

The author discusses a symptom complex of pain in the extremities following trauma involving nerves and blood vessels. Causalgia arises from a variety of injuries, including blows, crushes, fractures, puncture wounds, and animal bites. The mechanism by which the pain is produced is not definitely known but is thought to be the result of irritation of nerves in blood vessel walls, the vessels themselves often supplying nerve trunks. At any rate, it has been shown that the pain can be abolished by cutting off sympathetic impulses from the affected part. This can be done by sympathetic block by procaine.

NAIDE.

Bradley, S. E., and Parker, B.: The Hemodynamic Effects of Angiotonin in Normal Man. J. Clin. Investigation **20:** 715, 1941.

Cardiac output, mean arterial pressure, peripheral resistance, and efficient elasticity modulus have been determined following intravenous administration of angiotonin.

In all experiments, mean arterial pressure and peripheral resistance rose sharply. The pulse pressure tended to widen. With one exception, the efficient elasticity modulus rose sharply. Cardiac output fell as a result of a marked bradycardia. There was little change in stroke volume and, where a change occurred, it was in the direction of a decrease. Response to small single injections and to continuous intravenous infusions differed only in the absence of bradycardia in the latter.

Kymoroentgenogram and cardiocairogram studies revealed little change in heart size. However, there was present a consistent decrease in amplitude of ventricular waves.

It is concluded that angiotonin acts directly upon the musculature of the cardiovascular system, producing arteriolar vasoconstriction and possibly increased "cardia tone." Whether the distensibility of the central arterial reservoir is specifically decreased by angiotonin, or whether the observed change is attributable simply to increased distention of the central arteries, cannot be answered with certainty from the present data.

AUTHORS.

Wilkins, R. W., and Duncan, C. N.: The Nature of the Arterial Hypertension Produced in Normal Subjects by the Administration of Angiotonin. J. Clin. Investigation **20:** 721, 1941.

Angiotonin administered intravenously in normal subjects produces arterial hypertension which can be controlled by regulating the rate of administration.

This arterial hypertension is accompanied by an increase of venous pressure and frequently by other signs of "myocardial failure," including (a) decrease in vital capacity, (b) increase in circulation time, (c) decrease in cardiac output, and (d) increase in cardiac size. There is bradycardia, probably vagal in origin. Spinal fluid pressure is not significantly altered. The electrocardiogram reveals no important changes except bradycardia. The temperature of the skin usually decreases but remains responsive to alterations of body temperature. Blood flow measured plethysmographically in the limbs tends to decrease but remains

under the control of the sympathetic nervous system. Reactive-hyperemia blood flow (measured during full local vasodilatation produced by a five-minute period of arterial occlusion) increases with the rise of arterial pressure. The pressor response to the cold test of Hines and Brown is not altered during the hypertension. Mild symptoms of dizziness, substernal oppression, headache, nausea, or palpitation may be noted. The effects subside four to ten minutes after the cessation of administration, whether by single injection or by continuous infusion. Injected intradermally, angiotonin produces local blanching of the skin. Injected intra-arterially, it produces vasoconstriction in the muscular parts supplied by the artery.

AUTHORS.

Kirk, R. C., and Kilpatrick, E. M.: Ventricular Paroxysmal Tachycardia From Adrenalin and Sinus Standstill From Intravenous Quinidine in a Case of Coronary Occlusion. Ohio State M. J. 37: 437, 1941.

A case of coronary occlusion is presented which developed ventricular tachycardia following the use of adrenalin chloride in a digitalized heart. Efforts to restore normal rhythm by intravenous quinidine were followed by sinus arrest and sudden death. An autopsy disclosed an old anterior coronary occlusion with a recent posterior coronary occlusion complicated by a large mesenteric infarction.

AUTHORS.

Bonnell, R. W., Pritchett, C. P., and Hardin, T. E.: Treatment of Angina Pectoris and Coronary Artery Disease With Sex Hormones. Ohio State M. J. 37: 554, 1941.

Twenty-three patients with coronary artery disease, twenty-one of them having angina pectoris, were treated with sex hormones. Clinical improvement was noted in twenty-two of the twenty-three patients. Both estrogens and androgens were used.

Experimental evidence is cited which indicates that the sex hormones have a vasodilating property. It is thought that the improvement in this series of patients is due to a vasodilating property of the sex hormones acting on the coronary circulation.

AUTHORS.

Evans, G.: The Effect of Insulin on Cardiac and Liver Glycogen. Am. J. Physiol. 134: 798, 1941.

Rats were injected intravenously with glucose with or without insulin. Cardiac glycogen was found to be increased by glucose, but not further increased by the addition of insulin.

In the animals injected with glucose, the liver glycogen was found to be lowered by insulin and progressively so as the dose was increased; the effect occurs even during hyperglycemia; it is not mediated by the adrenal. Possible explanations are discussed.

AUTHOR.

American Heart Association, Inc.

1790 BROADWAY AT 58TH STREET, NEW YORK, N. Y.

DR. PAUL D. WHITE
President

DR. ROY W. SCOTT
Vice-President

DR. T. HOMER COFFEN
Treasurer

DR. HOWARD B. SPRAGUE
Secretary

BOARD OF DIRECTORS

•DR. EDGAR V. ALLEN	Rochester, Minn.	•DR. EDWIN P. MAYNARD, JR.	Brooklyn
DR. T. HOMER COFFEN	Portland, Ore.	•DR. THOMAS M. McMILLAN	Philadelphia
DR. CLARENCE DE LA CHAPELLE	New York City	DR. JONATHAN MEAKINS	Montreal
DR. HUGH FARRIS,	St. John, N. B., Canada	DR. E. STERLING NICHOL	Miami
DR. NORMAN E. FREEMAN	Philadelphia	DR. FRANKLIN R. NUZUM	Santa Barbara
DR. TINSLEY R. HARRISON,	Winston-Salem, N. C.	•DR. ROY W. SCOTT	Cleveland
DR. GEORGE R. HERRMANN	Galveston	DR. FRED M. SMITH	Iowa City
DR. T. DUCKETT JONES	Boston	•DR. HOWARD B. SPRAGUE	Boston
•DR. WILLIAM J. KERR	San Francisco	DR. WILLIAM D. STROUD	Philadelphia
DR. EMANUEL LIBMAN	New York City	•DR. PAUL D. WHITE	Boston
DR. DREW LUTEN	St. Louis	DR. FRANK N. WILSON	Ann Arbor
DR. GILBERT MARQUARDT	Chicago	•DR. IRVING S. WRIGHT	New York City
•DR. H. M. MARVIN	New Haven	DR. WALLACE M. YATER	Washington, D. C.

DR. H. M. MARVIN, *Chairman, Executive Committee and Acting Executive Secretary*
ANNA S. WRIGHT, *Office Secretary*
TELEPHONE CIRCLE 5-8000

THE American Heart Association is the only national organization devoted to educational work relating to diseases of the heart. Its activities are under the control and guidance of a Board of Directors composed of twenty-seven eminent physicians who represent every portion of the country.

A central office is maintained for the coordination and distribution of important information. From it there issues a steady stream of books, pamphlets, charts, films, lantern slides, and similar educational material concerned with the recognition, prevention, or treatment of diseases of the heart, which are now the leading cause of death in the United States. The AMERICAN HEART JOURNAL is under the editorial supervision of the Association.

The Section for the Study of the Peripheral Circulation was organized in 1935 for the purpose of stimulating interest in investigation of all types of diseases of the blood and lymph vessels and of problems concerning the circulation of blood and lymph. Any physician or investigator may become a member of the section after election to the American Heart Association and payment of dues to that organization.

The income from membership and donations provides the sole financial support of the Association. Lack of adequate funds seriously hampers more intensive educational activity and the support of important investigative work.

Annual membership is $5.00. Journal membership at $11.00 includes a year's subscription to the AMERICAN HEART JOURNAL (January-December) and annual membership in the Association. The Journal alone is $10.00 per year.

The Association earnestly solicits your support and suggestions for its work. Membership application blanks will be sent on request. Donations will be gratefully received and promptly acknowledged.

•*Executive Committee.*